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A correlation between carotid arterial wall elasticity and plaque instability as a prognostic factor of restenosis after surgical treatment of internal carotid artery stenosis

Korelacja pomiędzy elastycznością ściany tętnicy szyjnej a niestabilnością blaszki miażdżycowej jako czynnik prognostyczny wystąpienia restenozy po operacji zwężenia tętnicy szyjnej wewnętrznej

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elasticity, carotid plaque, restenosis

Słowa kluczowe
elastyczność, blaszka miażdżycowa, nawrotowe zwężenie

Summary

Introduction. Carotid endarterectomy is one of the most frequent procedures in vascular surgery. One of the most serious early and late problems after carotid endarterectomy is restenosis. The literature seems to underestimate the role of atherosclerotic plaque morphology as a factor of carotid artery restenosis. Patients with carotid artery atherosclerosis reveal a decreased elasticity of the *intima-media* complex, which results in a higher stiffness of the vascular wall.

Aim. The aim of the study was to assess a correlation between arterial elasticity and stability of the atherosclerotic plaque in patients with restenosis after internal carotid artery endarterectomy.

Material and methods. 180 patients qualified on the basis of typical indications based on the ultrasound examination underwent classic carotid artery endarterectomy. Restenosis was monitored by an ultrasound examination at 6 and 12 months after surgery. Elasticity of carotid arteries was measured with an apparatus called Vascular Echo Doppler. Morphology of the atherosclerotic plaque was assessed on the basis of the ultrasound image analysis with the use of Adobe Photoshop software.

Results. The plaque GSM median was significantly lower with a higher α coefficient measured a year after the surgery ($p = -0.16$; $p < 0.05$; $N = 180$), although it was not significantly correlated with α coefficient measured before the surgery ($p = 0.05$; p = n.s.; $N = 180$). This means that an increase in vascular wall stiffness, and resulting increase in α coefficient, is accompanied by a decrease in GSM of the atherosclerotic plaque, which is less calcified, and therefore less stable. Patients with an unstable atherosclerotic process reveal a higher risk of restenosis of the operated artery within 12 months.

Conclusions. A decrease in atherosclerotic plaque stability is correlated with an increased stiffness of common carotid arteries, which constitutes a higher additional risk of development of restenosis.

Streszczenie

Wstęp. Udrożnienie tętnic szyjnych należy do najczęściej wykonywanych operacji w chirurgii naczyniowej. Jednym z ważniejszych problemów wczesnych i odległych po endarterektomii tętnic szyjnych są ich nawrotowe zwężenia. Niedocenionym w literaturze czynnikiem nawrotowego zwężenia tętnic szyjnych wydaje się być rola morfologii blaszki miażdżycowej. U pacjentów z miażdżycą tętnicy szyjnej wewnętrznej stwierdza się spadek elastyczności kompleksu *intima-media*, a co za tym idzie większą sztywność ściany naczynia.

Cel pracy. Celem badania było określenie zależności pomiędzy elastycznością tętnic a stabilnością blaszki miażdżycowej u pacjentów z restenozą po operacjach udrożnienia tętnicy szyjnej wewnętrznej.

Materiał i metody. U 180 pacjentów kwalifikowanych na podstawie klasycznych wskazań opartych na badaniu USG, wykonano klasyczną endarterektomię tętnicy szyjnej. Zjawisko restenozy badano za pomocą USG po 6 i 12 miesiącach od operacji. Pomiar elastyczności tętnic szyjnych wykonywano za pomocą aparatu o nazwie Vascular Echo

Conflict of interest
Konflikt interesów
None
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Doppler. Do oceny morfologii blaszki miażdżycowej wykorzystano analizę obrazu USG za pomocą programu Adobe Photoshop.

Wyniki. Mediana GSM dla blaszki miażdżycowej była istotnie niższa wraz z wyższym współczynnikiem α mierzonym rok po operacji ($p = -0,16$; $p < 0,05$; $N = 180$), choć nie była istotnie związana ze współczynnikiem α mierzonym przed operacją ($p = 0,05$; $p =$ n.i.; $N = 180$). Oznacza to, iż wraz ze wzrostem sztywności ściany naczynia, a co za tym idzie – ze wzrostem współczynnika α, maleje wartość GSM blaszki miażdżycowej, która jest mniej uwapniona, a zatem mniej stabilna. U pacjentów z niestabilnym procesem miażdżycowym występuje większe ryzyko w ciągu 12 miesięcy pojawienia się nawrotowego zwężenia operowanej tętnicy.

Wnioski. Zmniejszenie stabilności blaszki miażdżycowej koreluje ze zwiększoną sztywnością ścian tętnic szyjnych wspólnych, co stanowi zwiększone dodatkowe ryzyko wystąpienia restenozy.

INTRODUCTION

Carotid endarterectomy is one of the most frequent procedures in vascular surgery. One of the most serious early and late problems after carotid endarterectomy is restenosis (1). Currently, despite well-developed imaging diagnosis and knowledge of mechanisms of atherosclerotic lesion formation, the mechanism of restenosis is still unclear. The literature seems to underestimate the role of atherosclerotic plaque morphology as a factor of carotid artery restenosis. The unstable form of the atherosclerotic plaque is related to a chronic inflammatory process taking place within the plaque. The process involves abnormal functioning of vascular endothelium, accumulation of inflammatory cells, including macrophages filled with LDL lipoproteins, and overgrowth of connective tissue (2). Patients with carotid artery atherosclerosis reveal a decreased elasticity of the *intima-media* complex, which results in a higher stiffness of the vascular wall (3). In the future, measurement of carotid artery elasticity may become a marker of post-operative stenosis development after endarterectomy of carotid arteries and other peripheral vessels.

AIM

The aim of the study was to assess a correlation between arterial elasticity and stability of the atherosclerotic plaque in patients with restenosis after internal carotid artery endarterectomy.

MATERIAL AND METHODS

Material

After clinical assessment and informed consent, 90 patients were qualified for the study and they underwent classic carotid artery endarterectomy at the Clinic of Vascular Surgery and Angiology of the Post-Graduate Medical Education Centre (CMKP).

A standard technique (CEA with direct occlusion) was used in carotid artery endarterectomy. The exclusion criteria comprised other endarterectomy techniques, e.g. patching or vivisection. Stitches at the site of artery incision were made of 6-0 non-absorbable, uniform (monofilament) thread. Heparin (3-5 thousand HNF) was administered during the procedure. After the surgery, the patients received acetylsalicylic acid (Acard) at the dose of 75 mg daily. In order to exclude early restenosis related to the technique itself, ultrasonographic monitoring of the anastomotic connection was used in each case.

This group included subjects with symptomatic atherosclerosis of carotid arteries, according to the recommendations of the NASCET and ECST studies, i.e.:

- symptomatic ICA stenosis above 50% (past episodes of contralateral amaurosis fugax during TIA, RIND, PRIND, or stroke from the stenotic side),
- asymptomatic stenosis above 70% with accompanying lesions,
- ICA stenosis above 70% in patients qualified for major vascular procedures (abdominal aortic aneurysm, surgery of Leriche syndrome or cardiac surgery with extracorporeal circulation).

Exclusion criteria:

1. Atheromatous lesions of subclavian arteries – prevent real measurement of arterial pressure on the arm.
2. Unstable hypertension – high parameters of arterial pressure on examination.
3. Cardiac arrhythmia – prevents pulse wave recording and analysing data by measurement apparatus.
4. Diabetes – a factor that has a significant effect on increased vascular stiffness.

Method

Vascular Echo Doppler (VED) apparatus (fig. 1) developed at the IPPT-PAN Ultrasound Centre was used in the study for non-invasive assessment of haemodynamic parameters of the circulatory system. It comprises a measurement module with a connected PC, whose memory stores the measurement data. The head of the measurement module consists of an ultrasonic part of 6.7 MHz frequency, which allows tracking an instant change of artery diameter by 7 μm, and a Doppler part containing an ultrasonic bidirectional continuous wave flowmeter of 4.5 MHz frequency (6). The equipment allows for a non-invasive measurement of carotid artery elasticity, where the basis for the analysis is a logarithmic correlation between the artery diameter and blood pressure (7). After applying this correlation logarithmic elasticity coefficient α was formulated.

$$\alpha = \frac{D_{min}}{D_{max} - D_{min}} \ln\left(\frac{P_s}{P_d}\right)$$

D_{min} – minimum artery diameter, D_{max} – maximum artery diameter and corresponding, P_s – systolic pressure, P_d – diastolic pressure

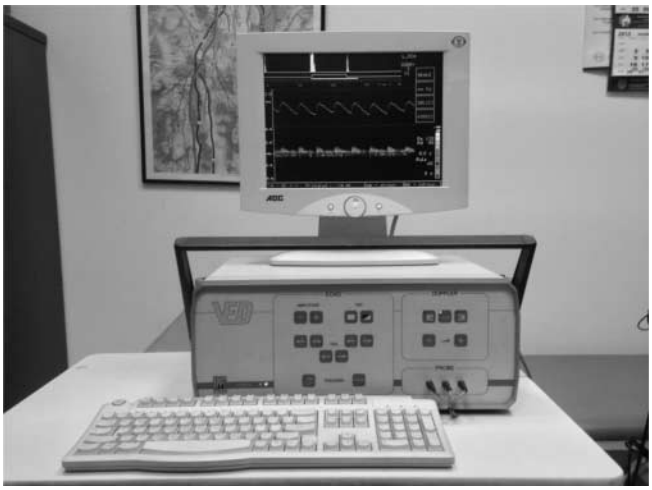

Fig. 1. VED (Vascular Echo Doppler) measurement kit

Technique of GSM median analysis (Adobe Photoshop software)

A method was used for ultrasound analysis with the Adobe Photoshop software. Image analysis was divided in two stages.

The first stage involves image normalization and the second stage involves calculation of the normalized image histogram.

The procedure of the registered ultrasound image normalization runs as follows:

- the analysed image is opened in the Adobe Photoshop software (fig. 2),
- the first reference area including the arterial lumen is marked (blood), see figure 3,
- m^1 median of the pixel values of the first reference area is calculated with the use of the histogram function from the "image" menu,
- the second reference area including the arterial wall is marked,
- m^2 median of the pixel values of the second reference area is calculated with the use of the histogram function from the "image" menu,
- normalization of values of all pixels included in the ultrasound image is performed with the use of the "adjust" function – curves from the "image" menu. All the pixels with a value lower than m^1 median from the first reference area have a value of 0 in the resulting image. All the pixels with a value higher than m^2 median from the second reference area have a value of 190 in the resulting image. The value of pixels from the (m^1, m^2) range is rescaled in a linear fashion to the (0.190) range.

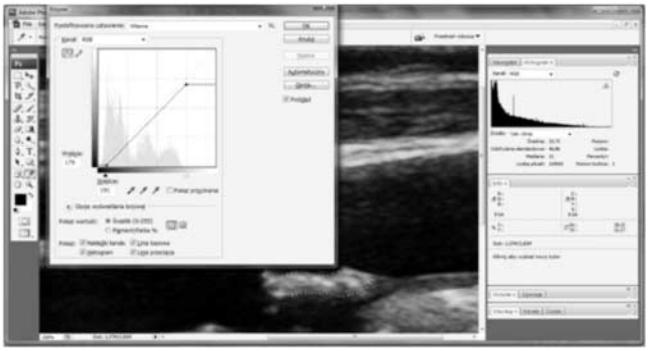

Fig. 2. Curve adjustment window from the Adobe Photoshop software. The horizontal axis shows a grayscale in the original image and the values on the diagram correspond to the values of pixels in the resulting image

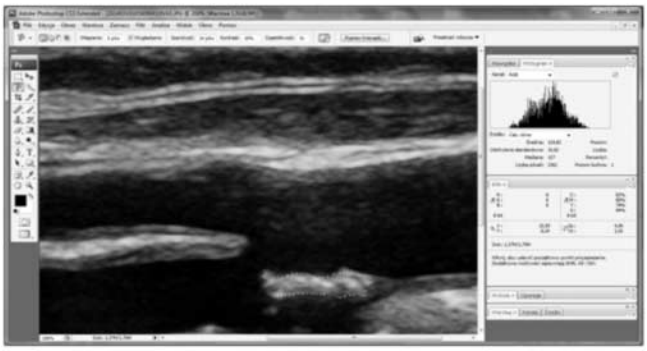

Fig. 3. Exemplary windows from the Adobe Photoshop showing the analysed ultrasound image and a histogram of the area containing the plaque image

After normalization of the image parameters, median of pixels comprising the analysed area is calculated. A histogram function from the "image" menu of the Adobe Photoshop is used for this purpose. The calculated median allows for classification of a plaque into a specific category.

RESULTS

The plaque GSM median was significantly lower with a higher α-O measured a year after surgery ($p = -0.16$; $p < 0.05$; $N = 180$), although it was not significantly correlated with α-O measured before surgery ($p = 0.05$; p = n.s.; $N = 180$). The correlation between the plaque GSM median and α-O was significantly stronger after a year than before surgery ($Z = 3.77$; $p < 0.01$).

Plaque GSM median was not significantly correlated with preoperative α-NO ($p = -0.11$; p = n.i.; $N = 180$), nor with α-NO measured a year after the surgery ($p = 0.09$; p = n.i.; $N = 180$). Although the change in the correlation strength was significant ($Z = 4.30$; $p < 0.01$), interpretation of this change seems to be unjustified, since none of the above plaque GSM median with α-NO was not statistically significant.

Thickness of *intima-media* was not significantly correlated with the level of α-O, neither prior to surgery ($p = -0.01$; p = n.i.; $N = 180$), nor a year after the surgery ($p = -0.07$; p = n.i.; $N = 180$). Thickness of *intima-media* was not significantly correlated with the level of α-NO, either, neither prior to surgery ($p = -0.08$;

p = n.i.; N = 175), nor after the surgery (p = -0.08; p = n.i.; N = 175). The measurement time alone does not significantly affect correlations between the analysed variables, since no statistically significant differences were observed between the obtained correlation coefficients.

This means that an increase in vascular wall stiffness, and resulting increase in α coefficient, is accompanied by a decrease in GSM of the atherosclerotic plaque, which is less calcified, and therefore less stable. Time measurement has a significant influence on the correlation between the analysed parameters. Patients with an unstable atherosclerotic process reveal a higher risk of restenosis of the operated artery within 12 months (fig. 4 and 5). This means that an increase in wall stiffness of the unoperated vessel, related to an increase in α coefficient, does not cause a correlation with the plaque GSM of the operated artery. Although such a correlation is not present, time measurement has a significant influence on the relationship between the analysed parameters.

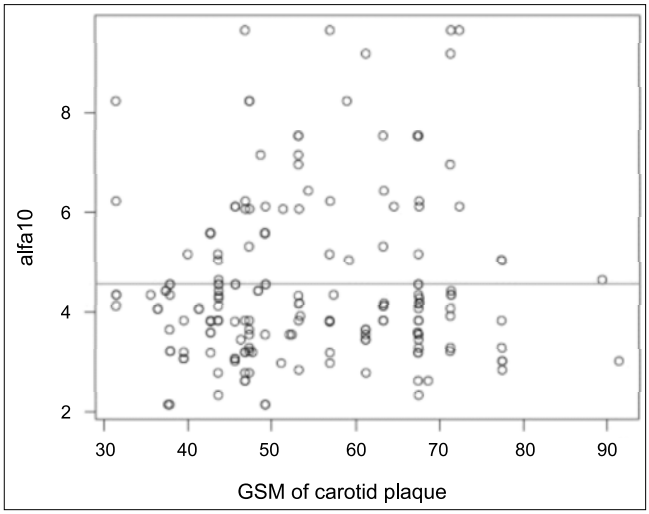

Fig. 4. A correlation between alpha10 coefficient and the plaque GSM value

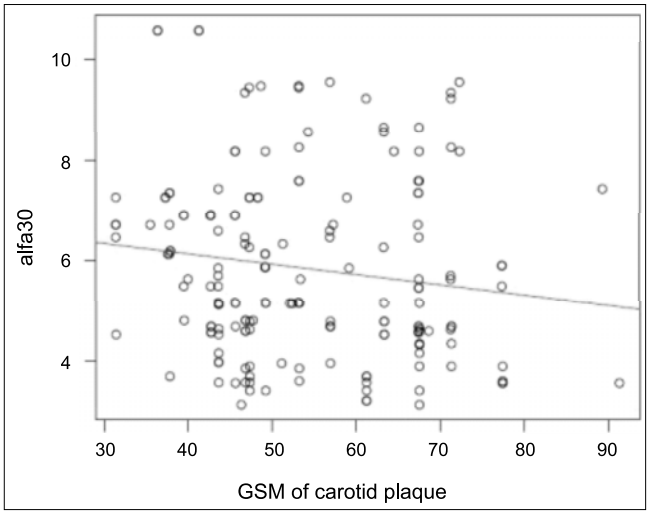

Fig. 5. A correlation between alpha30 coefficient and the plaque GSM value

The plaque GSM median was significantly lower with a higher α on the operated side, measured a year after the operation, while it was correlated with α on the unoperated side. The correlation between the plaque GSM median and α on the operated side was significantly stronger after a year than before the surgery. *Intima-media* thickness was not significantly correlated with the level of α, neither before the surgery nor a year after the surgery on neither side.

This means that an increase in vascular wall stiffness, and resulting increase in α coefficient, is accompanied by a decrease in GSM of the atherosclerotic plaque, which is less calcified, and therefore less stable. Time measurement has a significant influence on the correlation between the analysed parameters. Patients with an unstable atherosclerotic process reveal a higher risk of restenosis of the operated artery within 12 months.

DISCUSSION

The literature seems to underestimate the role of atherosclerotic plaque morphology as a factor of carotid artery restenosis. Madycki et Staszkiewicz emphasises the importance of inflammatory factors affecting the atherosclerotic plaque stability, and in consequence development of carotid artery restenosis (4). One of the most important mechanisms leading to development of restenosis after endarterectomy is inflammation caused by a surgical injury of the vessel and proliferation of a new internal membrane (5, 6). It is assumed that the proliferation is stimulated by inflammatory cells, i.e. monocytes/macrophages (7), since the blood often contains activated leukocytes (especially monocytes and granulocytes), platelets, adhesion molecules, aggregates of monocytes and platelets (8, 9) and increased interleukin-6 (IL-6) level (9). On the uncovered internal vascular membrane, monocytes undergo intensive and early accumulation and transformation in activated macrophages (10). These cells produce mediators of inflammation which stimulate release of cytokines (tumour necrosis factor – TNF (IL-1, IL-2, IL-6, IL-8)), growth factors (platelet-derived growth factor – PDGF), angiogenic factors (*vascular endothelial growth factor* – VEGF), adhesion molecules and free radicals (11). Production of biologically active mediators of inflammation stimulates migration and proliferation of smooth muscle cells, leading to hyperplasia of internal membrane and restenosis (12). Histology of the primary atherosclerotic plaque seems to be significant, as well. Studies conducted so far have revealed that patients with increased level of lipids and macrophages develop primary unstable and symptomatic plaque which is associated with increased incidence of restenosis. Patients with a reduced level of lipids and macrophages more often reveal a stable plaque, which does not stimulate development of restenosis (13, 14).

Studies conducted so far have revealed that the atheromatous plaque of asymptomatic patients is more stable and causes a lower inflammatory response. The lipid nucleus is smaller and the risk of restenosis

is reduced (15). The author of this study has obtained similar results. The results indicate that an increased level of α coefficient is accompanied by an increased level of plaque GSM. A comparison of both these correlation coefficients revealed that they reveal statistically significant differences. These means that after 12 months the correlation between the plaque GSM median and elasticity coefficient α is significantly stronger than before the procedure. A decrease in atherosclerotic plaque stability is correlated with an increased stiffness of common carotid arteries and a higher risk of development of restenosis.

The new approach to assessment of changes in arterial elasticity in diagnosis of early pathological changes of the cardiovascular system plays a more and more important role. Increase in wall stiffens is related among other things to development of hypertension. It is of high importance for early prevention and treatment of patients with increased risk factors and hereditary burden.

CONCLUSIONS

A decrease in atherosclerotic plaque stability is correlated with an increased stiffness of common carotid arteries, which constitutes a higher additional risk of development of restenosis. The measurement of carotid arterial elasticity could become in future a marker of rise postoperative restenosis after carotid endarterectomy arteries and other peripheral vessels.

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