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IMPAIRMENT OF ENDOTHELIUM-DEPENDENT VASODILATATION AND HYPERHOMOCYSTEINEMIA: PROGNOSTIC IMPLICATIONS OF ENDOTHELIAL DYSFUNCTION AFTER CAROTID ENDARTERECTOMY

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ABSTRACT

Objective: To evaluate and compare pre- and post-patch (p-CEA) and eversion carotid endarterectomy (e-CEA) markers of endothelial dysfunction in order to improve the diagnosis, surgical results of patients with carotid artery disease. **Materials and methods:** From October 2014 to October 2019, we examined 87 patients who underwent p-CEA (n=38) and p-CEA (n=49) at our medical center. Preoperative flow-mediated dilation (FMD) of brachial artery and pre- and immediate postoperative homocysteine level were compared between groups. **Results:** In the preoperative period, the impairment of endothelium-dependent vasodilatation and level of homocysteine of a higher than >10 mmol/l appeared to be experienced in 77 (88,5%) and 82 (94,2%) patients, respectively. In patients of the p-CEA group, the average FMD of the brachial artery was 5,67±1,54%, and 5,51±1,64% which was significantly lower than those of the e-CEA of 6,85±1,70% and 6,13±1,75% at 30 and 60 seconds post-cuff release, respectively ($p<0,05$). On day 6 after the operation, the homocysteine concentration increased compared to the preoperative level from 15,80±4,32 to 18,4±4,2 μmol/l ($p<0,05$) in the p-CEA group. In contrast, a preoperative homocysteine level of 13,10±3,15 μmol/l reached up to 14,2±5,6 μmol/l in the e-CEA group without significant difference ($p>0,05$). **Conclusion:** In the preoperative period, the flow-mediated dilation test showed better result in favor of e-CEA when compared to p-CEA. In the postoperative period, the growth of the homocysteine level was observed in the p-CEA group in contrast to e-CEA. Further study will be required to detect the precise association of hyperhomocysteinemia with suboptimal hemodynamic parameters of p-CEA.

KEYWORDS: *endothelial dysfunction, carotid endarterectomy, flow-mediated dilation, hyperhomocysteinemia*.

INTRODUCTION

Cerebro-vascular stroke as the result of atherosclerotic disease of the carotid arteries (stenosis, occlusion) is the third most common cause of death in industrialized countries, the most common neurological diagnosis that requires hospitalization, as well as the leading cause of long-term disability.[1] In the elderly, the increased incidence of cerebro-vascular stroke is associated with carotid stenosis. It is known that the age over 50 years increases the risk of cerebro-vascular stroke four times, and age over 59 years increases the same for even 8 times.[2,3] In this setting, two carotid endarterectomy techniques are commonly used in the treatment of carotid stenosis: carotid endarterectomy with conventional patch closure and carotid endarterectomy by eversion. Both techniques have comparable low rates of morbidity and mortality.[4,5] The potential advantage of e-CEA is the fact that placing the patch at the same it is not necessary.[6,7]

Endothelial dysfunction (ED), which is characterized by an impairment of endothelium-dependent vasodilatation, is an early event in the development of cardiovascular disease. Jiang et al., Cheng et al. reported that hyperhomocysteinemia (HHcy) is associated with ED and increased risk of atherosclerosis and thrombosis.[8,9] For these reasons, in addition to the traditional risk factors, both the World Health Organization and the Health Ministry agreed to consider HHcy, a strong contributor for cardiovascular disease.[10] Endothelial function is often quantified by flow-mediated dilation (FMD), which represents the endothelium-dependent relaxation of a conduit artery-typically the brachial artery – due to an increased blood flow. Brachial artery reactivity is a frequently used non-invasive ultrasonographic assessment of FMD that indicates endothelium-dependent response to shear stress.[11]

The aim of study was to examine and compare pre- and post-p-CEA and e-CEA markers of ED in order to improve the diagnosis, surgical results of patients with carotid artery disease.

MATERIAL AND METHODS

After Institutional Review Board approval, a retrospective review was performed between October 2014 and October 2019. All patients undergoing CEA at Bukhara branch of the Republican research center of emergency medical care were enrolled (87 patients) and divided into p-CEA (n=38 operation) and e-CEA (n=49 operation) groups. p-CEA was more commonly used for long and severe lesions and e-CEA was preferred by experienced surgeons. Patient demographics are given in Table 1.

Table 1: Patient demographics.

Variable	*n* (%) or mean ± SD
Age (years)	52,6±5,6
Sex (M/F)	51/36 (58,5/41,5)
Hypertension	76 (87,3)
Ischemic heart disease	53 (56,4)
Diabetes	11 (11,7)
Chronic obstructive pulmonary disease	16 (17,0)
Smoking history	34 (36,2)
Body mass index >25kg/m^2	33 (35,1)

Brachial artery FMD has been shown to correlate with measures of coronary endothelial function and impairment that is a predictor of cerebro- and cardiovascular diseases.[12] This technique has been extensively used with very good reproducibility and low observer variability. of 94 patients, 87 (38 patients of the p-CEA group and 49 - of the e-CEA) were checked for endothelium-dependent relaxation of the brachial artery. The brachial artery was scanned in the longitudinal section using an SSI 5000 Instrument with a 7, 5 MHz linear array transducer. Image acquisition was gated with an ECG R-wave so that images were captured at end diastole in each cardiac cycle. Recording of brachial artery were followed by inflation of a cuff to suprasystolic pressure (40 to 50 mmHg above systolic pressure) for 5 minutes as suggested by findings in Corretti et al.[13] Then the brachial artery diameter was imaged and recorded for 3 minutes using the 3D Doppler mode. Consequently, the cuff is released and after 30 sec of velocity recording, the ultrasound was switched to B-Mode. The following parameters were measured from the resulting time sequence of brachial artery diameter: mean baseline brachial artery diameter (D_{BL}) measured in millimeters; peak FMD measured in percentage and calculated as:

(Hyperemia diameter (D_{max}) - Baseline diameter (D_{BL})/ Baseline diameter (D_{BL})) *100 The normal reaction of the brachial artery was considered to be its dilation by more than 10% of the initial diameter on the background of reactive hyperemia. A lesser value or vasoconstriction was regarded as a pathological reaction.

On top of that plasma homocysteine (Hcy) level was checked. Hcy was determined in blood plasma by the enzyme-linked immunosorbent assay (normal range 8–12 μmol/l). Basing on the fact that the concentration of Hcy more than 10 μmol/L by the authors[14] is considered as an independent risk factor for thrombosis and embolism of blood vessels, we used this value as a threshold value in the development of ED and, accordingly, the progression of atherosclerosis at the site of carotid artery reconstruction.

Statistical analysis

Statistical analysis was performed with the SPSS version 22.0 program (SPSS Inc. Chicago IL, USA). Continuous variables were reported as means with standard deviations. The normality of distribution was checked with the Shapiro-Wilk test. Comparison was achieved with Student t-test. The relationship between two variables was evaluated with the Pearson's correlation coefficient. The Mann-Whitney U and Spearmen correlation test was used when the dependent variable did not normally distribute.

RESULTS

Regarding the obtained data, the impairment of endothelium-dependent vasodilatation was found in 77 (88, 5%) patients with diffuse atherosclerotic lesion. In patients of the p-CEA group, the average increase in the diameter of the brachial artery was 5,67±1,54%, and 5,51±1,64% which was significantly lower than those of the e-CEA: 6,85±1,70% and 6,13±1,75% at 30 and 60 seconds post-cuff release, respectively (p<0,05) (Fig. 1).

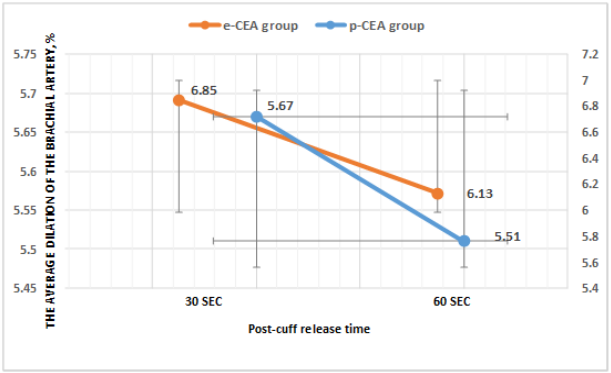

Figure 1: Dilation of the brachial artery at 30 and 60 seconds post-cuff release.

The correlation analysis revealed in both groups the inverse relationship between FMD and diabetes mellitus, age, body mass index, the thickness of the intima-media complex of the carotid artery (Table 2).

Table 2: Relationship of brachial artery dilation and cardiovascular risk factors.

Risk factors	Correlation coefficient, *r*	*p*
Total cholesterol	- 0,19	0,672
Diabetes mellitus	- 0,41	<0,001
Age	- 0,32	0,296
Body mass index >25	-0,27	0,252
Intima-media thickness >9 mm	- 0,34	<0,001

The excess of the Hcy concentration threshold (>10 mmol/l) as an independent risk factor for cerebrovascular disease [14] was identified in 82 (94,2%) patients with diffuse atherosclerotic lesion. The mean level of Hcy in the p-CEA group was 15,80±4,32 µmol/l. Of the whole p-CEA group, in 16 (42,1%) of 38 patients, the Hcy level exceeded 15 µmol/l. In the e-CEA group, the mean Hcy level was 13,10±3,15 µmol/l. Of those, 13 (26,5%) patients had a higher Hcy level than 15 µmol/l (Fig.2). Thus, it was found that the concentration of Hcy in the p-CEA group of patients was significantly higher than that of the e-CEA (p<0,05).

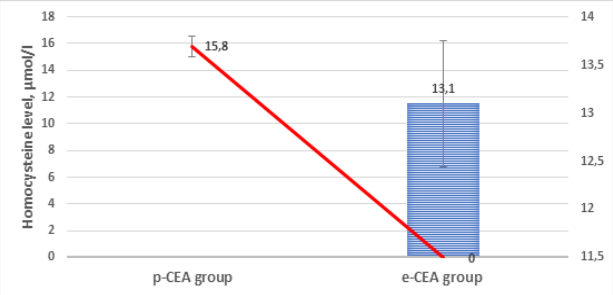

Figure 2: Homocysteine level after carotid endarterectomy.

The level of Hcy showed a positive correlation to some risk factors of cardiovascular disease, particularly to the level of total cholesterol and intima-media thickness of carotid artery.

Table 3: Relationship of homocysteine level and cardiovascular risk factors.

Risk factors	Correlation coefficient, *r*	*p*
Total cholesterol	0,38	0,004
Diabetes mellitus	0,47	0,626
Age	0,12	0,52
Body mass index >25	0,14	0,532
Intima-media thickness	0,56	0,008

On day 6 after the operation, the Hcy concentration was rechecked. In p-CEA group, the postoperative Hcy concentration increased compared to the preoperative level to 18, 4±4,2 µmol/l (p<0,05). In contrast, Hcy level reached up to 14, 2±5,6 µmol/l in e-CEA group without statistical significance (p>0,05) (Fig. 3).

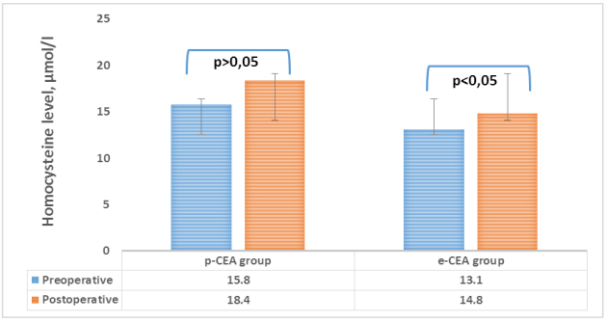

Figure 3: Comparative level of homocysteine before and after carotid endarterectomy.

DISCUSSION

In the past four years, several retrospective studies have demonstrated an association between ED and cerebro- and cardiovascular events.[15] In this setting, Celermajer et al[11] were the first to adopt a noninvasive assessment of FMD in the brachial or femoral artery to measure endothelial function that is the result of stimulation of vasoactive substances released by or that interact with the vascular endothelium. In the present study, we determined that the impairment of endothelium-dependent vasodilatation appeared to be experienced in 77 (88,5%) patients with diffuse atherosclerotic lesion before carotid endarterectomy. The latter test yielded better result in favor of e-CEA group as compared to p-CEA group.

The next finding of our study was the preoperative Hcy of a higher than >10 mmol/l level in 82 (94,2%) patients with diffuse atherosclerotic lesion. Similar data have been reported elsewhere. HHcy seems to be an independent risk factor for cerebrovascular disease [16], and, moreover, is related with atherosclerosis and cardiovascular disease.[10] Hongzhi Luo et al. found that HHcy may have a great impact on the pathogenesis of carotid artery thrombosis, dissection. The photogenic mechanism remains unknown, but on the basis remains that the consideration that HHcy promotes oxidative stress, accelerates vascular smooth muscle cell migration, adventitial collagen accumulation, and neointima formation .[17] Moretti et al reported the postulation that Hcy has a causative role in the determination of neurological damages due to its neurotoxic effect and to its direct or indirect vascular and endothelium induced pro-inflammatory effect as HHcy relates with both stroke, ischemic or hemorrhagic, and intracranial hemorrhage incidence, independent of long-recognized factors such as hyperlipidemia, hypertension, diabetes mellitus, and smoking.[14]

Furthermore, we found that there was an increase in the concentration of Hcy in the p-CEA group (p<0,05) postoperatively which is probably due to the suboptimal hemodynamic parameter of an overlaid patch in comparison with the e-CEA group. Some studies used computational fluid dynamics to investigate the blood flow regime in the post-CEA region in patient-specific geometries. Harrison et al.[18] showed that incorporation of a patch indeed increases the artery diameter, but it results with larger areas of low-wall shear stress and high-oscillatory shear index at the bifurcation, and therefore, its benefit is questionable. Similarly, Guerciotti et al.[19] and Domanin et al.[20] also analyzed low-wall shear stress, vorticity, time-averaged high-oscillatory shear index, and relative residence time. According to all these studies, cases with primary suture resulted with better hemodynamic parameters and smaller areas of disturbed flow in comparison with patch graft cases. Especially, oscillatory shear index value was generally higher in patch graft cases with respect to primary closure, especially for high carotids or when the

arteriotomy is mainly at the bulb region. Therefore, the relationship of the HHcy to comparative poor hemodynamic parameters of p-CEA should be further studied to disclose the complex mechanism.

CONCLUSION

To summarize, more intensive ED markers was revealed in patients of both groups with diffuse atherosclerotic lesions. In the preoperative period, the FMD test showed better result in favor of e-CEA when compared to p-CEA. In the postoperative period, the growth of the Hcy level was observed in the p-CEA group in contrast to e-CEA. Finally, further study is warranted to unravel the precise association of HHcy with suboptimal hemodynamic parameters of p-CEA.

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