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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Incomplete Circle of Willis and cerebrovascular reactivity in asymptomatic patients before and after carotid endarterectomy

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SUMMARY

Introduction/Objective Circle of Willis (CoW) provides the most significant collateral flow in the presence of significant stenosis or occlusion of internal carotid artery. In terms of collateral flow "incomplete" type and "complete" type of CoW can be recognized. Patients with carotid artery disease with incomplete CoW have lower cerebrovascular reactivity and higher risk for stroke. Cerebrovascular reactivity refers to the residual capacity of dilatation of cerebral blood vessels in the condition of insufficient blood flow. In this study we analyzed changes in cerebrovascular reactivity after carotid endarterectomy in asymptomatic patients with respect to complete and incomplete CoW morphology.

Methods In this study in 97 patients with asymptomatic carotid artery disease we measured cerebrovascular reactivity before and after carotid endarterectomy by using method of "apnea test" and "breath-holding index" (BHI). Patients were divided into two following groups: patients with "complete" CoW and "incomplete" CoW based on non-contrast magnetic resonance angio performed previously to the operation. Descriptive statistics, univariate analysis, and ANOVA for comparison of BHI values between groups were used.

Results The results showed significant increase in cerebrovascular reactivity at the side of stenosis in both groups of patients with complete CoW (BHI value increased from 0.897 to 1.090; $F(1.65) = 30.788$, $p < 0.0005$, parc. $\eta^2 = 0.321$) and incomplete CoW (BHI value increased from 0.690 to 1.010; $F(1.27) = 62.318$, $p < 0.0005$, parc. $\eta^2 = 0.698$) and the more significant increase in the group of incomplete CoW compared to the group with complete CoW ($F(1.92) = 4.557$, $p = 0.035$, parc. $\eta^2 = 0.047$)

Conclusion In most asymptomatic patients, cerebrovascular reactivity restores to normal following carotid endarterectomy. Parameters of cerebrovascular reactivity are lower in patients with incomplete CoW and the increase after carotid endarterectomy is more significant in such patients.

Keywords: breath-holding index; extracranial carotid disease; internal cerebral artery; asymptomatic carotid patients risk stratification

INTRODUCTION

Circle of Willis (CoW) provides the most significant collateral flow in the presence of significant stenosis or occlusion of internal carotid artery (ICA). Anterior collateral segment of CoW (ACA1, AcomA) is a connection between opposite carotid arteries and posterior collateral segment (ACP1, AcomP) provides collateral from posterior cerebral circulation [1].

Morphology of CoW can be evaluated by non-contrast enhanced magnetic resonance angiography and it depicts the functional status of collateral flow [2]. Although there is a number of CoW morphology types, in terms of collateral flow "incomplete" and "complete" types of CoW can be recognized. Contrary to the "complete" CoW that depicts normal CoW morphology, "incomplete" CoW refers to the hypoplasia or occlusion of anterior and posterior collateral segment and consequent absents of collateral flow provided by CoW.

In the presence of significant ICA stenosis, incomplete CoW can be associated with impaired cerebral blood flow, reduction of cerebral autoregulation decreased circulatory reserve and low cerebrovascular reactivity leading to increased stroke risk [3]. Cerebrovascular reactivity describes the capacity of adaptation of cerebral blood flow as a reaction to different stimuli. If insufficient cerebral blood flow is present, blood vessels are maximally dilated, and the residual capacity to increase blood flow is limited.

In this study, we analyzed changes in cerebrovascular reactivity after carotid endarterectomy in asymptomatic patients with respect to complete and incomplete CoW morphology.

METHODS

The research included 97 out of 171 patients, who were operated from asymptomatic extracranial carotid stenosis from January 2017 to June 2019. Prior to the operation, all patients underwent Duplex Ultrasound Examination (DUS) od carotid arteries and at least one of the following imaging: Magnetic Resonance Imaging (MRI) and Magnetic Resonance

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Angiography (MRA) (Siemens 1.5T, Siemens Healthineers, Erlanger, Germany) or Computed Tomography Imaging (CT) and Computed Tomography Angiography (CTA) (64 or 128 lines) of head and neck. MRI and MRA with three-dimensional time of flight (3D TOF) sequence for examination of extracranial portion of carotid and vertebral arteries and CoW and intracranial arteries was mandatory for patients who were included into the study.

Based on aforementioned diagnostic procedures, inclusion and exclusion criteria for this study were defined: patients with unilateral carotid disease (contralateral carotid stenosis was less than 50%) were included, with no significant lesions on intracranial portion of carotid arteries, vertebral and basilar arteries and cerebral arteries and no evidence of "silent brain infarctions" larger than one centimeter. Patients who were presented with insufficient data, poor insonation window for measurement of cerebrovascular reactivity or low compliance with the procedure, patients who refused to give their written consent were also excluded from the study.

We collected preoperative data on patients' general characteristics, risk factors and comorbidity: age, gender, presence of hypertension, diabetes, smoking, hyperlipoproteinemia, history of ischemic heart disease or heart failure, left ventricle hypertrophy, significant heart valve diseases, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease and peripheral artery disease (PAD). Assessment of clinical cardiologist has been provided.

Morphology of CoW was determined based on 3D TOF sequence of MRA. By morphology, patients were classified into two groups:

1. Group of patients with "complete CoW" in which all arteries of CoW were shown on 3D TOF sequence MRA (67 patients – 69%)
2. Group of patients with incomplete CoW: underdeveloped or occluded anterior (ACA1, AcomA) and posterior (ACP1, AcomP) collateral segment of CoW (30 patients – 31%)

Degree of ICA stenosis was estimated by DUS based on European Carotid Surgery Trial criteria and two groups of patients were recognized: group of patients with 75–84% ICA stenosis and group of patients with 85–99% ICA stenosis.

All patients underwent operation under general anesthesia; one of the following techniques was used: Carotid Endarterectomy (CEA) with patch plasty and intraluminal shunt protection or Eversion endarterectomy (EEA). Standardized perioperative protocol included administration of clopidogrel 75 mg at least five days prior to the operation with no discontinuation for the operation day, administration of statins starting at least 30 days before the operation. In the postoperative period, strict blood pressure control was indicated, with the aim to maintain systolic blood pressure below 160 mmHg.

For estimation of cerebrovascular reactivity, we used "Apnea test" method, previously described by Silvestrini et al. [4]. In Apnea test, the patients were asked to hold their breath for 30 seconds, and consequent increase in blood CO_2 is used as a stimulus for dilatation of cerebral blood vessels. The increase in blood flow during apnea test is registered with Transcranial Doppler ultrasound (TCD) (Multidop X4, DWL Elektronische Systeme Compumedics GmbH, Singer, Germany) with 2 MHz probe and Sonara Viasys version 04 (Vyaire Medical Inc., Mettawa, IL, USA) with 2MHz probe on proximal portion of the middle cerebral artery. As a result of the test the breath-holding index (BHI) is calculated as ratio between stimulated (CBF30 sec) and basal cerebral blood flow (CBFbasal):

$$BHI = ((CBF30\,sec - CBFbasal)/CBFbasal)/(sec/100).$$

The "cut-off" point for normal finding was set on 0.69. In this research apnea test was done to all patients a day before and a month after surgery.

We compared BHI values before and after surgery in groups of patients with complete and incomplete CoW for both sides: ipsilateral and contralateral to stenosis.

Statistical analysis included descriptive statistics: mean value, frequency (count) and relative frequency (percentage) for categorical data; comparative statistics included univariate analysis of variables with odd's ratio calculation; differences between BHI values before and after surgery in groups of patients with complete and incomplete CoW for both sides: ipsilateral and contralateral to stenosis has been analyzed by ANOVA. SPSS Statistics ver. 25.0 (IBM Inc. Armonk, NY, USA) was used.

Subjects' written consents have been obtained. All studies have been approved by the ethics committee of the Clinical Centre of Vojvodina and the Faculty of Medicine of the University of Novi Sad, and conforms to the legal standards. In most of the patients, MR examinations were done as a part of the project "Registration of New Ischemic Lesions with Magnetic Resonance Imaging Before and After Carotid Endarterectomy and Carotid Stenting", financed by the Provincial Secretariat for Higher Education and Scientific Research of Vojvodina. Subjects' written consent have been approved by the ethics Committee of the Clinical Centre of Vojvodina and Faculty of Medicine of the University of Novi Sad and conforms to the legal standards.

RESULTS

A total of 97 asymptomatic patients with ICA stenosis, 75 males, and 24 females, aged 54–79 years, median value 66.33, underwent carotid endarterectomy due to extracranial carotid disease. Both techniques of carotid endarterectomy with patch angioplasty and intraluminal protection (44%) and eversion endarterectomy (54%) were used depending on preferences of surgeon performing the operation, all under general anesthesia. We did not register any major perioperative adverse event (stroke or death) and we registered one postoperative case of acute coronary syndrome that was successfully treated by percutaneous coronary angioplasty. Patients' general characteristics and comorbidities with respect to complete and incomplete CoW morphology are shown in Table 1.

In both groups of patients with complete CoW and incomplete CoW degree of ICA stenosis (patients were classified into groups 75–84% and 85–99% stenosis) was equally distributed, as shown in Table 2.

Table 1. Distribution of patients' general characteristics, risk factors, and comorbidity in the groups with complete and incomplete Circle of Willis (CoW)

Variables	Complete CoW	Incomplete CoW	Total	OR	p value
Circle of Willis	70	27	97	-	-
Age (median value)	67.9	65,9	66.33	-	0.465
Males	78%	76%	76%	1.105	0.8734
Hypertension	83%	87%	86%	0.792	0.811
Diabetes mellitus	38%	36%	36.5%	1.131	0.819
Smoking	50%	53%	51%	1.077	0.870
Hyperlipoproteinemi	58%	73%	62%	0.882	0.759
Ishaemic heart disease or heart failure	27%	26%	27%	0.939	0.903
Left ventricle hypertrophy	22%	23%	22%	1.047	0.932
Significant heart valve disease	0%	1%	1%	7.981	0.207
Atrial fibrillation or other arythmia	11%	15%	12%	1.291	0.697
Chronic kiddney disease	4.2%	3.7%	4.1%	0.827	0.871
Chronic obstructive pulmonary disease	8.5%	11%	9%	1.333	0.700
Peripheral artery disease	13%	7%	11%	0.629	0.562

Table 2. Degree of Internal Carotid Artery stenosis by European Carotid Surgery Trial criteria estimated by duplex ultrasound in the groups of patients with complete and incomplete Circle of Willis (CoW)

CoW morphology	Degree of stenosis		Total	p value
	75–84%	85–99%		
Incomplete CoW	21	9	30	0.78
Complete CoW	45	22	68	
Total	66	31	97	

Preoperative values of BHI at the side of stenosis were 0.897 for the group of patients with complete CoW and 0.617 in the group of patients with incomplete CoW. In 34% of patients with complete CoW and 70% of patients with incomplete CoW preoperative BHI value were lower than previously defined "cut-off" value of 0.69. After the operation BHI values were 1.09 for group of patients with complete CoW and 1.01 in group of patients with incomplete CoW. Only 5.8% of patients with complete CoW and 6.7 % with incomplete CoW had postoperative BHI value less than 0.69.

Observing BHI values lower than 0.69 as pathological, we registered significant reduction of number of pathological findings of BHI level after the operation in the group of patients with incomplete CoW (63.3%) compared to the group of patients with complete CoW (28.2%) and the difference was statistically significant ($p = 0.0016$, OR = 4.36 CI 1.75–10.78) as shown in Figures 1a and 1b.

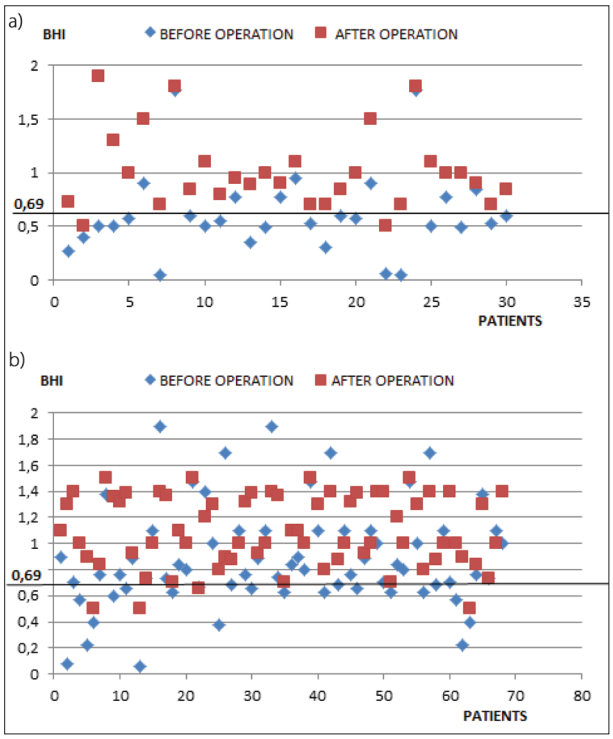

Figure 1. Breath-holding index values before and after operation in asymptomatic patients with a) incomplete Circle of Willis; b) complete CoW

By using ANOVA, we tested primary effects of two following variables: morphology of CoW ("complete" and "incomplete" CoW) and operation status (before and after surgery) on BHI values. It was determined that there was a significant difference in BHI values before the surgery between groups of patients with complete and incomplete CoW, $F(1.94) = 16.208$, $p < 0.001$, parc. $\eta^2 = 0.150$ and significant difference in BHI values between same groups after the surgery, $F(1.94) = 4.134$, $p < 0.05$, parc. $\eta^2 = 0.043$. We found significant influence of carotid endarterectomy on the BHI values in the group of patients with incomplete CoW, $F(1.27) = 62.318$, $p < 0.0005$, parc. $\eta^2 = 0.698$ and in the group of patients with complete CoW, $F(1.65) = 30.788$, $p < 0.0005$, parc. $\eta^2 = 0.321$, as shown in Figure 2a.

By using ANOVA, we tested interaction effect of following variables: morphology of CoW ("complete" and "incomplete" CoW) and operation status (before and after surgery) on BHI values. There was a significant interaction between the completeness of the CoW and operation status and their impact on the level of BHI, $F(1.92) = 4.557$, $p = 0\ 035$, parc. $\eta^2 = 0.047$. More significant increase in BHI value was registered in group of patients with incomplete CoW after the operation compared to patients with complete CoW. The difference proved to be statistically significant for $p = 0.035$. Therefore, carotid endarterectomy affected the patients with incomplete CoW more, in terms of improvement of cerebrovascular reactivity, as shown in Figure 2a.

For the side opposite to stenosis, ANOVA showed significant difference in BHI value before and after operation in both groups ($F = 7.357$, $p = 0.008$, parc. $\eta^2 = 0.072$), but no difference between the groups ($F = 0.831$, $p = 0.34$, parc. $\eta^2 = 0.009$), as shown in Figure 2b.

DISCUSION

In asymptomatic significant ICA stenosis, revascularization is indicated only in low risk patients, who feature increased risk of stroke [5]. In this respect, investigation of

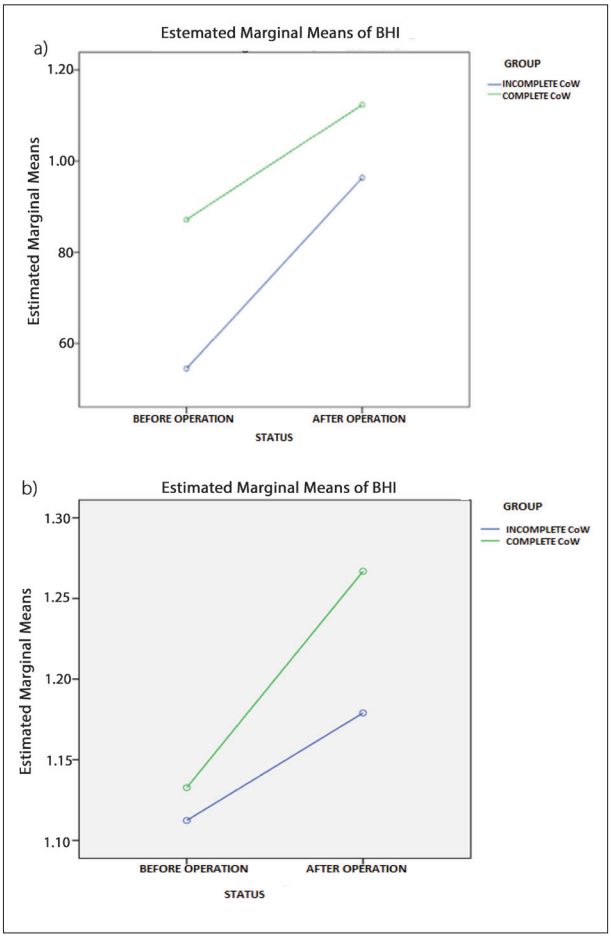

Figure 2. Estimated marginal means of breath-holding index before and after operation in asymptomatic patients with complete and incomplete Circle of Willis (CoW) at the a) operated side; b) contralateral side

cerebrovascular reactivity in asymptomatic patients has been recognized in up-to-date guidelines in preoperative assessment and risk stratification of patients with carotid artery stenosis [6]. Low cerebrovascular reactivity means that the cerebral arteries are already dilated to the maximum due to low cerebral perfusion and there is a limited reserve of adaptation of cerebral flow. In asymptomatic patients with significant carotid artery stenosis reduced cerebrovascular reactivity increases risk of stroke 13–25% per year [7–11]. Decreased circulatory reserve and lack of collateralization may increase the risk of stroke by the mechanism of impaired hemodynamics and due to the fact that arterio-arterial embolization from diseased carotid artery occurs more often in the zone of reduced circulatory reserve [12, 13].

Association of incomplete CoW finding on non-contrast enhanced magnetic resonance angiography and low cerebrovascular reserve has been documented as well [14]. Non-contrast enhanced magnetic resonance angiography that was used in our research, represents functional morphology of CoW as it displays only blood flow within the vessels [2]. Although numerous types of CoW morphology have been described, simplification to "complete" and "incomplete" CoW has been accepted for easier use in clinical practice [15]. It is evidenced that 25–30% of asymptomatic patients and 45–60% of symptomatic patients with carotid artery disease have incomplete CoW [16]. In symptomatic patients with significant ICA stenosis, if the incomplete CoW is present, there is an increased annual risk of stroke up to 13–17% [17, 18]. For asymptomatic patients with ICA stenosis, there is a lack of data from controlled prospective studies [19]. Retrospective post-hoc analyzes of a SMART group showed increased but not statistically significant risk of stroke in patients with "incomplete" CoW [14].

Our study showed that in patients with incomplete CoW, circulatory reserve at the side of ICA stenosis was significantly lower (median BHI = 0.62) compared to the patients whose MRA findings showed the complete CoW (BHI median = 0.88). Ass well BHI at the side of ICA stenosis was lower compared to the side opposite to the stenosis (BHI median = 1, 09). BHI in the group of patients with incomplete CoW tended to be lower than the proposed cut-off value for normal findings which is 0.69 [4].

Operative treatment resulted in the significant increase in BHI at the side of the stenosis both in groups of patients with complete and incomplete CoW. We registered both significant improvement circulatory reserve and normalization of the findings in the majority of patients in which BHI was below the threshold of 0.69. Such effect indicates that the revascularization of stenosed ICA removes the cause of impaired circulatory reserve and reduced vasomotor reactivity. More beneficial effect of surgical treatment we found to be in asymptomatic patients with incomplete CoW with more significant increase of BHI. For the opposed side, we found a trend of greater postoperative increase in BHI value in the group with complete CoW, which can be explained by the phenomenon of "stealing" from the healthy side over active collaterals that was present before the operation.

The literature emphasizes the importance of the effect of carotid endarterectomy on patients with extremely low parameters of cerebral vasoreactivity [20, 21]. Soinne et al. [22] founded beneficial effect of surgery only in symptomatic but not in asymptomatic patients. In aforementioned research, the asymptomatic patients were not stratified according to CoW morphology. A significant improvement of cerebrovascular reactivity after carotid endarterectomy in asymptomatic patients can be registered in both sides of brain [23, 24]. Surgical treatment of asymptomatic and symptomatic patients is followed by normalization of cerebrovascular reactivity and collateral flow in the CoW [25]. Improvement of cognitive function after carotid endarterectomy along with the improvement of cerebrovascular reactivity is emphasized [26]. Previously mentioned SMART study group was one of the rare studies that followed operated and non-operated asymptomatic patients with complete and incomplete CoW, still it was the retrospective study [14].

Apnea test and its modifications are easily available, and can be done in most vascular labs, it is also proved to be comparable to other methods of measurement of cerebrovascular reactivity [27]. Still there is a problem of its reliability especially in patients who are poorly compliant

with the procedure, which is recognized as a limitation of this study. Association of incomplete CoW and low cerebrovascular reserve is evident, as well as the effect of ICA revascularizations on cerebrovascular reactivity, but whether the presence of incomplete CoW can be observed as a risk feature in asymptomatic ICA stenosis is still to be debated.

CONCLUSIONS

In most asymptomatic patients, cerebrovascular reactivity restores to normal following carotid endarterectomy. Parameters of cerebrovascular reactivity are lower in patients with incomplete CoW and the increase after carotid endarterectomy is more significant in such patients. This suggests that carotid endarterectomy is more beneficial in asymptomatic patients with incomplete CoW in terms of cerebrovascular reactivity, but does it indicate clinical benefit in such patients (i.e. reduction of the risk of stroke) is yet to be approved by future prospective studies.

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Некомплетност Вилисовог прстена и цереброваскуларна реактивност код асимптоматских болесника пре и после каротидне ендартеректомије

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САЖЕТАК

Увод/Циљ Вилисов прстен представља најзначајнији колатерални пут којим се обезбеђује проток у хемисферама мозга код екстракранијалне каротидне стенозе или оклузије. У погледу присуства колатералног протока разликујемо комплетни и некомплетни Вилисов прстен. Болесници са екстракранијалном каротидном болешћу који имају некомплетан Вилисов прстен имају слабију цереброваскуларну реактивност и повишен ризик можданог удара. Цереброваскуларна реактивност описује резидуални капацитет за дилатацију церебралних крвних судова у условима можданe хипоперфузије.

Циљ ове студије био је да се утврде промене у цереброваскуларној реактивности после каротидне ендартеректомије код асимптоматских болесника са комплетним и некомплетним Вилисовим прстеном.

Методе Студија је укључила 97 болесника са асимптоматском каротидном екстракранијалном болешћу код којих смо одређивали цереброваскуларну реактивност методом апнеа теста пре и после каротидне ендартеректомије. Болесници су на основу налаза безконтрастне магнетне резонантне ангиографије били подељени у две групе: болесници са комплетним Вилисовим прстеном и болесници са некомплетним Вилисовим прстеном. Статистичка анализа подразумевала је дескриптивну статистику, униваријантну анализу и *ANOVA* за поређење параметара цереброваскуларне реактивности пре и после каротидне ендартеректомије.

Резултати Резултати су показали значајно повећање параметара цереброваскуларне реактивности на страни стенозе у обе групе болесника са комплетним Вилисовим прстеном (пораст *BHI* са 0,897 на 1,090; F (1,65) = 30,788, $p < 0,0005$, *parc.* $\eta^2 = 0,321$) и некомплетним Вилисовим прстеном (пораст *BHI* са 0,690 на 1,010; F (1,27) = 62,318, $p < 0,0005$, *parc.* $\eta^2 = 0,698$), при чему је пораст у групи са некомплетним Вилисовим прстеном био значајнији за $p = 0,035$ (F (1,92) = 4,557, *parc.* $\eta^2 = 0,047$).

Закључак Код већине асимптоматских болесника са каротидном болешћу каротидна ендартеректомија доводи до нормализације параметара цереброваскуларне реактивности. Цереброваскуларна реактивност је нижа код болесника који имају некомплетан Вилисов прстен, а пораст цереброваскуларне реактивности после операције израженији је код ових болесника.

Кључне речи: индекс задржавања даха; унутрашња каротидна артерија; екстракранијална каротидна болест; стратификација ризика код асимптоматских каротидних болесника