Research Article
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Multicenter Study of Resistant Arterial Hypertension Course after Classic and Eversion Carotid Endarterectomy

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AIM OF STUDY Analysis of the dynamics of resistant arterial hypertension (RAH) and the spectrum of adverse cardiovascular events in patients after classical carotid endarterectomy (CEE) with preservation of carotid body (CB) and eversion CEE with CB transection.

MATERIAL AND METHODS This cohort, comparative, retrospective, open-label study from January 2014 to December 2020 included 761 patients with hemodynamically significant stenosis of the internal carotid arteries (ICA) and RH lasting more than 3 years. Depending on the implemented revascularization strategy, 2 groups were formed: Group 1: 38.0% (n=289) — classical CEE with plasty of the reconstruction zone with a patch (made of diepoxy-treated xenopericardium or synthetic); Group 2: 62% (n=472) — eversion CEE with CB transection. To study the dynamics of systolic blood pressure (SBP) in the preoperative period for 4 days, and in the postoperative period, blood pressure was measured for 10 days (during the period when the patient was in intensive care - according to daily monitoring of blood pressure; in the department - 10 times per day, daily). The average SBP figures for all patients were taken into account when constructing a graph of BP fluctuations.

RESULTS In the postoperative period, the groups were comparable in the frequency of the following events: death (group 1: 0.34% (n=1), group 2: 0.63% (n=3); p=0.98; OR 0.54; 95% CI 0.05–5.21), myocardial infarction (group 1: 0.34% (n=1), group 2: 0.84% (n=4); p=0.71; OR 0, 40; 95% CI 0.04–3.65), ischemic stroke (group 1: 0.34% (n=1), group 2: 1.27% (n=6); p=0.36; OR 0.26; 95% CI 0.03–2.25), hemorrhagic transformation (group 1: 0%, group 2: 0.84% (n=4); p=0.29; OR 0.17; 95% CI 0.009–3.35). However, in terms of the number of all complications (death + myocardial infarction + ischemic stroke + hemorrhagic transformation) presented as a combined endpoint, patients after eversion CEE with CB transection were three times superior to classical surgery (group 1: 1.03% (n=3), group 2: 3.60% (n=17); p=0.05; OR 0.28; 95% CI 0.08–0.9).

CONCLUSION The choice of a revascularization strategy in patients with hemodynamically significant ICA stenosis should be personalized and based on the conclusion of a multidisciplinary consultation, and not only on the preferences of the operating surgeon. In patients with RH, it is more expedient to use classical CEE with plasty of the reconstruction zone with a patch in view of the preservation of the CB during this operation. The intersection of the latter with eversion CEE provokes labile hypertension, progression of RAH and a statistically significant increase in the number of all unfavorable cardiovascular events. Thus, the use of carotid body preserving CEE in patients with RAH confirms the therapeutic mechanism of this manipulation in achieving the target SBP level.

Keywords: carotid endarterectomy, classical carotid endarterectomy, eversion carotid endarterectomy, resistant arterial hypertension, arterial hypertension, labile arterial hypertension, patch, hemorrhagic transformation

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AH - arterial hypertension
BP - blood pressure
ASP - atherosclerotic plaque
ICA - internal carotid artery
TS - temporary shunt
CI - confidence interval
MI - myocardial infarction
CG - carotid glomus
CABG - coronary artery bypass grafting
CEE - carotid endarterectomy
LV - left ventricle
MFA - multifocal atherosclerosis
ECA - external carotid artery
ACVA - acute cerebrovascular accident
OR - odds ratio
PICS - post-infarction cardiosclerosis
RAH - resistant arterial hypertension
SBP - systolic blood pressure
DM - diabetes mellitus
HF - heart failure
TIA - transient ischemic attack
TSBCA - triplex scanning of brachiocephalic arteries
DUSG - Doppler ultrasonography
EF - ejection fraction
FC - functional class
COPD - chronic obstructive pulmonary disease
CRF - chronic renal failure
PCI - percutaneous coronary intervention

INTRODUCTION

Resistant arterial hypertension (RAH), according to the All-Russian Society of Cardiology and the Russian Medical Society for Arterial Hypertension, is a condition in which taking at least 3 antihypertensive drugs in combination with lifestyle changes (giving up bad habits, hypocholesterol diet, hyposalt diet, etc.) does not lead to normalization of blood pressure (BP) (target values 140/90 mm Hg) or achievement of these values is possible after the appointment of at least 4 antihypertensive drugs [1]. The latest guidelines from the European Society of Cardiology and the European Society of Hypertension for new treatments for hypertension — *"Device-based treatment"* different methods of RAH correction are considered. Of these,

ablation of the carotid glomus located in the bifurcation of the carotid arteries is proposed as one of the non-standard ones [2, 3]. However, a small series of observations and high risks of distal embolism do not allow this method to achieve the required level of evidence for routine use [2, 3]. In addition, the effect of this procedure in the presence of hemodynamically significant stenosis in the internal carotid artery (ICA) is not clear [2, 3]. It is known that after the removal of an atherosclerotic plaque (AP), the amplitude of the pulse oscillations of the vessel wall increases, which causes the activation of carotid glomus baroreceptors and a decrease in blood pressure [4]. It follows from this that ablation can be effective only in the absence of a stenotic process in the ICA, which is not additionally mentioned in the recommendations. Against this background, the contribution of the two most common types of carotid endarterectomy (CEE) to the treatment of patients with concomitant RAH is of interest - the classic one with plastic reconstruction of the reconstruction zone with a patch and eversion endarterectomy [5–9]. Both techniques involve the removal of ASP from carotid artery. However, during the first one, a longitudinal dissection of the ICA is performed without involving the carotid glomus (CG), and during the second one, the ICA is cut off from the bifurcation at the mouth, which inevitably leads to trauma to the CG. [5–9]. Considering the results of studies on the outcomes of glomus-sparing CEE, it follows that CG will aggravate the course of the postoperative period with a tendency to labile BP [10–14]. However, the results of such operations in patients with RAH have not yet been published.

The aim of this study was to analyze the dynamics of RAH and the spectrum of adverse cardiovascular events in patients after classical CEE with CG preservation and eversion CEA with CG clipping.

MATERIAL AND METHODS

This cohort comparative retrospective open study for the period from January 2014 to December 2020 included 761 patients with hemodynamically significant stenoses of the ICA and RAH for more than 3 years.

Depending on the revascularization strategy implemented, two groups were formed: group 1: 38.0% (n=289) — classical CEE with reconstruction area plasty with a patch (from diepoxy-treated xenopericardium or synthetic); Group 2: 62% (n=472) — eversion CEE with CG cutoff.

The inclusion criteria were: 1. Indications for CEA in accordance with current recommendations; 2. Presence of RAG; 3. RAG experience exceeding 3 years; 4. Absence of severe renal failure (glomerular filtration rate more than 80 ml / min / 1.73 m2, blood creatinine less than 90 μmol / l); 5. The absence of pathological conditions in the adrenal glands, including pheochromocytoma; 6. Absence of hemodynamically significant stenoses of the renal arteries; 7. Absence of contralateral stenotic lesion of the ICA; 8. Absence of diabetes mellitus (DM); 9. Отсутствие черепно-мозговой травмы; 10. Absence of the most acute and acute periods of ischemic stroke; 11. No planned simultaneous heart surgery in combination with CEE; 12. Absence of a planned hybrid operation: percutaneous coronary intervention (PCI) + CEE. The exclusion criteria implied indicators that did not satisfy the above inclusion points.

To study the dynamics of systolic blood pressure (SBP) in the preoperative period for 4 days, and in the postoperative period for 10 days, blood pressure was measured (during the patient's stay in intensive care - according to the data of daily monitoring of blood pressure; in the department - 10 times a day daily) . The average SBP figures for all patients were taken into account when plotting BP fluctuations.

The choice of revascularization strategy was carried out by a multidisciplinary council, including a cardiovascular surgeon, endovascular surgeon, neurosurgeon, cardiologist, neurologist, anesthesiologist, resuscitator.

The risk stratification for the development of postoperative complications and the severity of the comorbid background were assessed using a scale *EuroSCORE* II. The severity of coronary atherosclerosis was calculated using an interactive calculator *SYNTAX Score (www.syntaxscore.com)*. According to the severity of the lesion, the following gradation is distinguished on the basis of this calculator: low level of lesion (no more than 22 points), intermediate (23–32 points) and severe (no less than 33 points).

Visualization of atherosclerotic lesions of the brachiocephalic arteries was performed using Doppler ultrasound of the transcranial arteries (USDG), color triplex scanning of the brachiocephalic arteries (TSBCA) (using a linear transducer with a frequency of 7–7.5 MHz) on devices "*MySono U6-RUS*" *(Samsung Electronics)*, "*Philips Affiniti* 30". If a significant stenosis was detected according to the TSCA data, an increase in the blood flow velocity according to the ultrasound data, in the presence of an unstable ABP in the ICA, multislice computed tomography with angiography (MSCT with angiography) was performed. The degree of stenosis was determined by the classification *NASCET*.

Compensatory possibilities of cerebral blood flow during CEE were assessed as follows. When the level of SBP was not more than 160 mm Hg. we performed a pharmacological increase in blood pressure to 190/100 mm Hg. Then 5,000 units of heparin were administered intravenously, arterial clamping was performed. Invasive measurement of retrograde pressure in the ICA was performed. When blood pressure was less than 60% of systemic, a temporary shunt (TS) was applied. During the operation, all patients underwent cerebral oximetry. With a decrease in oximetry values below 30% of the initial value, a IS was installed.

The control points were understood as the development of such adverse cardiovascular events as death, myocardial infarction (MI), acute cerebrovascular accident/transient ischemic attack (CVA/TIA), thrombosis in the reconstruction area, bleeding type 3*b* and higher on a scale *Bleeding Academic Research Consortium (BARC)*, combined endpoint (death + stroke/TIA + hemorrhagic transformation + MI). Visualization of the reconstruction zone was performed by ultrasound on the 3rd day after the operation.

The study was performed in accordance with the standards of good clinical practice *(Good Clinical Practice)* and the principles of the Declaration of Helsinki.

The type of distribution was determined using the Kolmogorov–Smirnov test. Groups were compared using the Mann-Whitney test and Pearson's χ-square with Yates correction. Differences were rated as significant, with $p<0,05$. The research results were processed using a package of applied programs *Graph Pad Prism (www.graphpad.com)*.

The groups were comparable in all clinical and anamnestic characteristics. The vast majority were male and older persons. Every fifth had a history of MI, every third had an ischemic stroke. The assessment of the stratification of the risk of complications and the severity of the comorbid background corresponded to the average severity on the scale *EuroSCORE* II (table. 1).

Table 1

Comparative clinical and anamnestic characteristics of patient groups

Indicator	Group 1, *n*=289	Group 2, *n*=472	*p*	Odds ratio	95% Confidence Interval
Age, *M±m*, years	65,3±3,1	65,4±4,0	0,45	–	–
Male, *n* (%)	215 (74,4)	339 (71,8)	0,49	1,14	0,81–1,58
CI 1–2 FC, *n* (%)	128 (44,3)	218 (46,2)	0,66	0,92	0,69–1,24
PICS, *n* (%)	54 (18,7)	86 (18,2)	0,94	1,03	0,70–1,50
COPD, *n* (%)	2 (0,7)	4 (0,8)	0,85	0,81	0,14–4,48
MFA with hemodynamically significant lesion of three arterial beds, *n* (%)	183 (63,3)	294 (62,3)	0,83	1,04	0,77–1,41
EF LV, *M±m*, %	58,8±4,1	58,2±6,0	0,32	–	–
LV aneurysm, *n* (%)	0	2 (0,4)	0,70	0,32	0,01–6,79
EuroSCORE II, *M±m*	2,5±0,7	2,6±1,0	0,41	–	–
history of PCI, *n* (%)	38 (13,1)	67 (14,2)	0,72	0,90	0,58–1,38
CS in history, *n* (%)	9 (3,1)	14 (2,9)	0,91	1,05	0,44–2,46
history of stroke/TIA, *n* (%)	90 (31,1)	146 (30,9)	0,98	1,01	0,73–1,38

Notes: CI — confidence interval; CABC — coronary artery bypass grafting; MFA — multifocal atherosclerosis; ACBA — acute cerebrovascular accident; OR — odds ratio; PICS — postinfarction cardiosclerosis; HF — heart failure; TIA — transient ischemic attack; LVEF — left ventricular ejection fraction; FC — functional class; COPD — chronic obstructive pulmonary disease; PCI — percutaneous coronary intervention

RESULTS

According to angiographic characteristics, the groups were also comparable. The presence in the vast majority of patients with unstable ASP and subocclusion of the ICA has become an indication for urgent CEA. Indicators of damage to the coronary bed, according to *SYNTAX score*, corresponded to a mild degree of severity. The time of clamping the ICA during the operation also did not differ (Table. 2).

Table 2

Angiographic and perioperative characteristics

Indicator	Group 1, *n*=289	Group 2, *n*=472	*p*	OR	95% CI
% stenosis of the ICA	89,4±7,7	85,6±9,1	0,26	–	–
Unstable ASP, *n* (%)	115 (39,8)	195 (41,3)	0,73	0,93	0,69–1,26
SYNTAX score taking into account myocardial revascularization in history, *M*±m	13,3±2,7	10,1±3,4	0,84	–	–
ICA clamping time, min	26,2±3,1	25,4±2,8	0,55	–	–

Notes: АСБ — atherosclerotic plaque; ICA — internal carotid artery; CI — confidence interval; ECA — external carotid artery; OR — odds ratio

In the postoperative period, the groups were comparable in terms of the frequency of all events. However, in terms of the number of all complications presented as a combined endpoint, patients after eversion CEE with CG transection were 3 times superior to classical surgery ($p = 0.05$, statistically significant). It should be noted that all adverse cardiovascular events in group 2 occurred against the background of postoperative hypertensive crisis and labile arterial hypertension (AH). (*max* MBP = 203,7±8,5 mm Hg) as the consequences of removing the CG.

When analyzing the dynamics of the severity of hypertension, the following was noted. If at the preoperative stage all patients had one or another degree of hypertension without reaching the target level of blood pressure, then at the time of discharge in the group of eversion CEE with crossing the CG, the number of patients with grade III increased statistically significantly. At the same time, after applying the classical CEE, 70.9% of the operated patients reached the target level of blood pressure.

This trend is also confirmed by the analysis of the graph of the SBP dynamics. However, it should be noted that on the 2nd–3rd day after CEE, in both groups, an increase in SBP was observed, which may be associated with an increase in edema and inflammation in the intervention area, followed by regression within 1–2 days (Fig.).

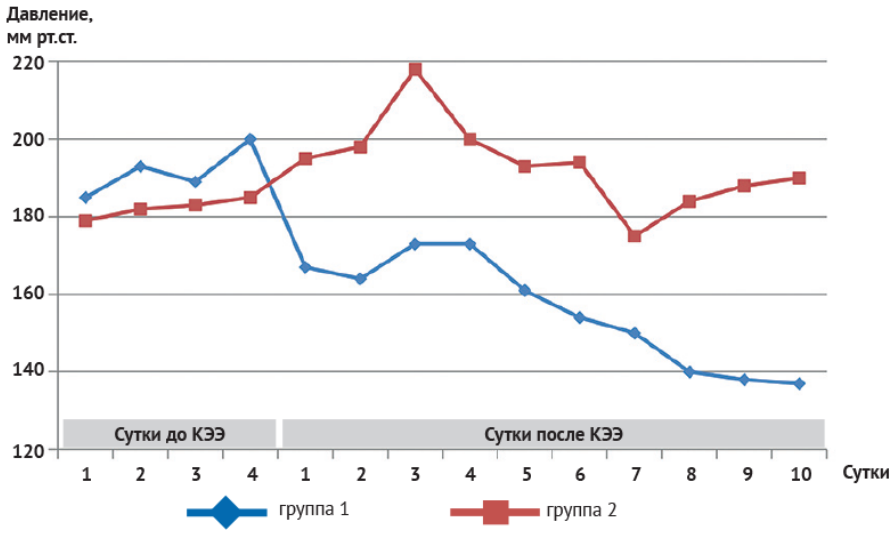

Figure. Graph of the dynamics of systolic blood pressure in the pre- and postoperative period
Note: CEA — carotid endarterectomy.

DISCUSSION

Analyzing the results of both methods of CEE, it is necessary to note the discrepancy between the obtained data and the available world literature. According to the vast majority of studies at the hospital stage of observation, the classical and eversion techniques have a comparable incidence of all adverse cardiovascular events, including the combined end point [5, 15–17]. However, it should be noted that these studies were carried out on continuous samples of patients, without taking into account RAH in history. At the same time, RAH with a hypertensive crisis at the onset of the postoperative period can cause the development of hemorrhagic transformation in the brain and other complications against the background of the course of multifocal atherosclerosis [1, 18–21]. A trend towards an insignificant increase in the frequency of cardiovascular accidents in our study was identified for all indicators in the group of eversion CEE with CG crossing (Table 3). In addition, only this cohort was diagnosed with the development of hemorrhagic transformation. Thus, the presence of RAH in patients with hemodynamically significant stenosis of the ICA should be considered as an indication for choosing a glomus-sparing surgical technique, which, in the framework of the present study, was the classical CEE with plasty of the reconstruction zone with a patch.

Table 3

Hospital results

Indicator	Group 1, *n*=289	Group 2, *n*=472	*p*	OR	95% CI
Death, *n* (%)	1 (0,34)	3 (0,63)	0,98	0,54	0,05–5,21
MI (non-fatal)), *n* (%)	1 (0,34)	4 (0,84)	0,71	0,40	0,04–3,65
ACVA/TIA (non-fatal), *n* (%)	1 (0,34)	6 (1,27)	0,36	0,26	0,03–2,25
Hemorrhagic transformation, *n* (%)	0	4 (0,84)	0,29	0,17	0,009–3,35
Bleeding type 3*b* and up on the scale *BARC*, *n* (%)	1 (0,34)	5 (1,05)	0,51	0,32	0,03–2,79
ICA thrombosis, *n* (%)	1 (0,34)	1 (0,21)	0,70	1,63	0,10–26,27
Combined Endpoint, *n* (%)	3 (1,03)	17 (3,60)	0,05	0,28	0,08–0,9

Notes: ICA — internal carotid artery; CI — confidence interval; MI — myocardial infarction; ADCC — acute disturbance of cerebral circulation; OR — odds ratio; TIA — transient ischemic attack

Another observation was that, despite the type of CEE, on the 2nd–3rd day after the operation, there was an increase in SBP (see figure). Further, in patients with preserved CG, it regresses and reaches the target level, and in patients with eversion CEE, SBP continues to grow. We associate this pattern with the development of an inflammatory process in the reconstruction zone, which, along with edema, excites CG and activates the sympathetic system. Subsequently, against the background of the relief of the inflammatory response, this factor ceases to be a trigger for the rise in SBP. A similar trend was proved by N.B. Kosacheva et al. and *M.M. Marrocco-Trischitta* in their works [4, 22]. It was even proposed to block CG with a local anesthetic to prevent the development of a hypertensive crisis [4]. However, this technique has not been widely adopted. The authors also demonstrated that the removal of ASP leads to a decrease in both SBP (from 145.1±14.7 to 135.6±12.3 mm Hg, p=0.02) and diastolic BP (from 83.3 ±10.2 to 78.1±9.7 mm Hg, p=0,02) [4]. This conclusion was presented by A.N. Vachev et al. In 87.6% of operated patients, persistent stabilization of blood pressure was achieved with target values in 65.7% patients [23]. At the same time, the number of patients with III degree of AH decreased statistically significantly to 5.8% (p<0,001) [23]. The results of our work showed a similar trend, however, in contrast to the above studies, we demonstrated the dynamics of indicators among patients with RAH, which became the novelty of this article.

Despite the fact that the mechanism of the work of CG, which consists in the connection of baroreceptors of the carotid bifurcation with the vasomotor center, has been repeatedly proven, there are works that refute this conclusion. So, E.V. Frolova, in the presence of RAH, purposefully performed an eversion CEE with crossing the CG [1]. Ultimately, this step led to the achievement of the target BP level in 66.7% of patients. The author did not explain the mechanism of this effect, only indicating that her results disagree with the conclusions of other studies [1]. In particular *S.A. Nouraei et al.* indicated a statistically significant increase in

blood pressure at the intersection of the CG (p<0,00001) [24]. A.A. Fokin cited evidence that CG injury is a trigger for labile hypertension and hypertensive crisis [25]. *M.M. Marrocco-Trischitta* concluded that the preservation of CG is a protective factor for the progression of AH [22]. *S. Demirel et al*. showed that after the eversion CEA, the SBP level increased statistically significantly (134 mm Hg vs. 126 mm Hg, p<0.0001) [26]. *M. Taurino et al*. compared the outcomes of the Chevalier technique and the eversion CEA with the intersection of the CG. It has also been proven that as a result of CG injury, critical levels of SBP are observed [27].

Thus, the vast majority of studies come to a consensus - the preservation of CG, no matter what method of CEE is used, prevents the formation of labile AH, hypertensive crisis with a milder course of the postoperative period, which also affects the frequency of adverse cardiovascular outcomes.

Table 4

The severity of arterial hypertension depending on the period and type of carotid endarterectomy

Degree of hypertension	Number of patients		*p*	OR	95% CI
	Before CEE	After CEE			
Classical CEE					
Achievement of the target level of BP, *n* (%)	0	205 (70,9)	<0,0001	0,0007	$4{,}378 \cdot 10^{-5}$ – 0,01152
I, *n* (%)	15 (5,2)	48 (16,6)	<0,0001	0,27	0,15–0,50
II, *n* (%)	161 (55,7)	15 (5,2)	<0,0001	21,3	12,1–37,59
III, *n* (%)	113 (39,1)	21 (7,3)	<0,0001	8,19	4,95–13,55
Eversion CEE					
Achievement of the target level of BP, *n* (%)	0	0	–	–	–
I, *n* (%)	32 (6,8)	8 (1,7)	0,0002	4,21	1,92–9,25
II, *n* (%)	304 (64,4)	240 (50,8)	<0,0001	1,74	1,34–2,27
III, *n* (%)	136 (28,8)	224 (47,5)	<0,0001	0,44	0,34–0,58

Notes: AH — arterial hypertension; BP — blood pressure; CI — confidence interval; CEA — carotid endarterectomy; OR — odds ratio

CONCLUSION

The choice of revascularization strategy in patients with hemodynamically significant stenosis of the internal carotid artery should be personalized and based on the conclusion of a multidisciplinary consultation, and not only on the preferences of the operating surgeon. In patients with resistant arterial hypertension, it is more reasonable to use a classic carotid endarterectomy with plastics of the reconstruction area with a patch due to the preservation of the carotid glomus during this operation. Intersection of the latter during eversion carotid endarterectomy provokes labile arterial hypertension, progression of resistant arterial hypertension and a statistically significant increase in the number of all adverse cardiovascular events. Thus, the use of glomus-sparing carotid endarterectomy in patients with resistant arterial hypertension confirms the therapeutic mechanism of this manipulation in achieving the target level of systolic blood pressure.

FINDINGS

1. When choosing the technique of carotid endarterectomy in patients with resistant arterial hypertension, preference should be given in favor of the classical operation.

2. Performing classical carotid endarterectomy allows a statistically significant (p<0.0001) reduction in the number of patients with II and III degrees of arterial hypertension.

3. When performing eversion carotid endarterectomy in patients with resistant arterial hypertension in the postoperative period, careful monitoring of blood pressure is required due to the presence of unstable hemodynamic parameters and a statistically significant (p<0.0001) increase in the number of patients with II and III degrees of arterial hypertension.

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