RESEARCH ARTICLE

Impact of Stent-Assisted Recanalization of Carotid Artery Stenosis on Brain Volume Changes

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ABSTRACT

Objective: The purpose of this study was to investigate the effect of recanalization on stenotic internal carotid artery on brain volume changes in stent applied patients.

Materials and Methods: Carotid stenting was performed in 17 patients with severe carotid artery stenosis between June 2013 and April 2014. High resolution 3D T1 weight images were obtained from each patient 24 hours before and 7.2 ± 3.6 months (mean ± standard deviation) after the procedure on a 3T magnetic resonance imaging scanner. Intracranial total cortical grey matter, total cortical white matter, white matter hypointensity, total intraventricular and subcortical grey matter volumes were assessed by FreeSurfer version 4.5.0.

Results: A significant reduction was found in total cortical white matter and subcortical grey matter volumes (p<0.05). A significant increase was found in white matter hypointensity and total intraventricular volumes after procedure (p<0.05). However, no statistical significant difference was found in total cortical grey matter volume before and after procedure (p=0.902).

Conclusion: The significant reduction in the postoperative intracranial total cortical white matter and subcortical grey matter volumes and the significant increase in the white matter hypointensity volume were considered to be secondary to neuronal damage. *J Clin Exp Invest 2016; 7(4): 283-289*

Key words: Brain volume changes, carotid stenosis; magnetic resonance imaging

INTRODUCTION

Patients with stenosis of internal carotid artery (ICA) have an annual stroke risk of 5-6% which increases to 70% if more stenosis occurs. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are the methods performed to avoid the potential risk of stroke [1].

In severe stenosis, cerebral perfusion might be reduced due to decreased blood supply. To diagnose cerebral microcirculationin patients with stenosis of ICA, several imaging techniques such as cervical and transcranial doppler, perfusion computed tomography (CT),

intracarotid xenonium injection and perfusion magnetic resonance imaging (MRI) are needed. However, post-CAS hemodynamic changes in cerebral perfusion are not yet clearly known [2].

MR image-guided surface or voxel-based brain analysis methods help to assess cerebral cortex thickness. FreeSurfer is one of the surface-based methods, which is most commonly used and is a frequently referred methodology in clinical trials [3]. It is an easy-to-use brain analysis software which provides accurate and automated image analysis [4]. To our knowledge, there are no published studies that investigated the effect of stent-assisted

recanalization on brain volume changes by using the software FreeSurfer.

In this study, we investigated the effect of recanalization on stenotic ICA on brain volume changes in stents applied patients by evaluating T1-weighted 3D MR images before and after the procedure.

METHODS

Patients

Carotid stenting was performed in 17 patients (9 on the left, 4 on the right side and 4 on both sides, 21 total stents) with severe ICA stenosis between June 2013 and April 2014. Severe stenosis is defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) as more >70% narrowing of the vessel [5]. Inclusion criteria were as follow; a history of carotid stenting with severe (more than 70%) carotid stenosis, a T1-weighted 3D MRIs before and after the procedure and cerebral ischemic risk. Patients not meeting these criteria were excluded. Fourteen males (82.4%) and 3 female were enrolled (17.6%). The mean degree of stenosis was 89.4±7.8% on the right side and 86.5±7.5 % on left side. The patients' mean age was 65.8 ± 5.7 years (age range 56-77 years). Table 1 shows the co-morbidities of all patients i.e. 88% of the patients had hypertension (n=15), 47% had coronary artery disease (n=8), 41% had smoking history (n=7), 18% had diabetes (n=3), 18% had a history of cerebrovascular event (n=3), and 12% hyperlipidemia (n=2). High resolution 3D T1-weighted images were acquired on a 3T MRI scanner using 32-channel head coil 24 hours before and an average of 7.18±3.6 months after the procedure (ranging from 2 to 12 months). Intracranial total cortical grey matter, total cortical white matter, white matter hypointensity, total intraventricular and subcortical grey matter volumes were assessed by using the software FreeSurfer version 4.5.0. Approval was obtained from the ethics committee before the study.

Interventional Technique

Informed consent was obtained from all patients that were scheduled for endovascular stent placement. Acetylsalicylic acid (Aspirin®; Bayer) 100-300 mg/day and clopidogrel (Plavix®;

Sanofi-Synthalebo) 75 mg/day p.o. was administered at least 72 hours prior to the procedure. Stenting was performed under sterile conditions and local anesthesia (2% prilocaine; Citanest, AstraZeneca) using a biplane, flat-panel angiography unit (AXIOM Artis FD Biplane Angiosuite; Siemens Medical Solutions). An 8F introducer was inserted into the right common femoral artery using the single-wall puncture technique. During the procedure, 5000-7000 units of heparin were administered intraarterially. Either right or left common carotid artery (CCA) was reached by using a guidewire (Roadrunner; Cook) and an 8F guiding catheter (Envoy; Cordis) depending on the stenosis site. Right or left ICA stenosis was determined on the angiographic images. The stenosis was crossed with a filter device (Emboshield NAV[6]; Abbott vascular). The filter was opened in the petrous portion of the ICA. After opening the filter, a 3x20 mm balloon (Empira; Cordis) was used for pre-dilatation. Then, a self-expanding nitinol-carotid stent [Protege stent (n=9); Covidien, Xact stent (n=7); Abbott vascular and Precise stent (n=5); Cordis] was placed into the ocluded segment. ICA reconstruction was obtained with 5x20 mm balloons (Viatrac 14 Plus; Abbott vascular and Aviator Plus; Cordis) after the stenting. The filter was removed from the petrous portion of the ICA and the femoral artery access site was closed with a vascular closure system (StarClose; Abbott vascular). Immediately after the procedure, 1000 U/hour intravenous heparin was administrated for 8 hours, followed by enoxaparine (Clexane®, Aventis) 0.6 ml/day s.c. for three days. No clinical deficit occurred in the patients following the successful endovascular treatment. Stable patients were discharged one day after operation and prescribed acetylsalicylic acid 100-300 mg/day for lifelong and clopidogrel 75 mg/day for 3-6 months.

Magnetic Resonance Imaging

Conventional axial, sagittal and coronal T1 and T2-weighted images were acquired on a 3T scanner (Achieva 3.0T Tx; Philips) using a 32-channel head coil. High resolution T1-weighted 3D images were acquired using 3D-FFE (three dimensional fast field echo) sequence with scan time of approximately 5.5 minutes. The parameters were as followed: repetition time (TR)/echo time (TE): 8.2/3.8, inversion time (TI):

1018 ms, number of signal averages (NSA): 1, flip angle: 8°, field of view (FOV): 240×240 mm, matrix: 240×240, slice voxel size: isovolumetric 1 mm, and 170 slices.

Morphometric Analyses

Images acquired by the high resolution MRI were transferred into a DICOM format for Macintosh-based computer. FreeSurfer4.5.0 software was used for morphometric analyses. First, distortions on the images caused by the patient movements and variations of brightness caused by the changes in the B1 field were corrected. Second, images were placed on the Talairach coordinate system which allowed for pre-labeling by using manually created standard brain templates. This led to the increased success of segmentation. Also errors caused by pathologies were reduced this way. Tabula was automatically deleted, and the rest was used as a brain mask for labeling and segmentation.

Outcomes of automatic deletion and segmentation were reviewed. If necessary; corrected and volume measurements were repeated by a specialist radiologist. Post-processing took approximately 8 hours in each patient. This way, measurements of total cortical grey matter, total cortical white matter, white matter hypointensity, total intraventricular and subcortical grey matter volumes were obtained and used in statistical analysis.
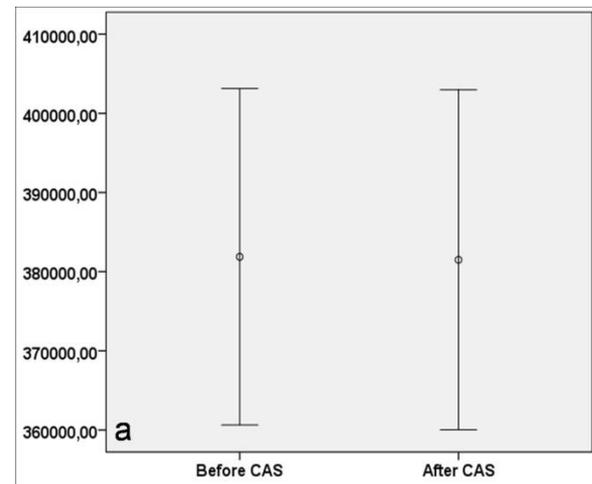
Statistical analyses

All statistical analyses were performed with SPSS 22.0 statistical program. Whether data demonstrated a normal distribution or not was determined using Shapiro-Wilk test. Descriptive values of variables were expressed as means, standard deviations, medians, minimums and maximums. Wilcoxon signed rank test and matched pairs t-test were used for group comparison. The level of significance was determined as 0.05.

RESULTS

After CAS, no statistical significant difference was observed in the total cortical grey matter volumes (p=0.902). The mean total cortical grey matter volume was 381875±41334 mm^3 before and 381496 ± 41757 mm^3 after CAS. On the other hand, a significant reduction was observed in the total cortical white matter and subcortical

grey matter volumes (p<0.05). The mean total cortical white matter and subcortical grey matter volumes were 428110±75521 mm^3 and 157333 ± 18077 mm^3 before and 412200±73801 mm^3 and 155154 ± 17297 mm^3 after CAS, respectively.

Figure 1. Graphical analyses of pre and post-CAS cerebral volumes: Total cortical grey matter volume.

A significant increase was observed in the total intraventricular and white matter hypointensity volumes (p<0.05). The median total intraventricular and white matter hypointensity volumes were (min-max) 30945 mm^3 (15944-57931) and 4591 mm^3 (1980-20464) before and 34967 mm^3 (19333-76057) and 6491 mm^3 (2571-22526) after CAS, respectively (Figures 1-5, Table 2).
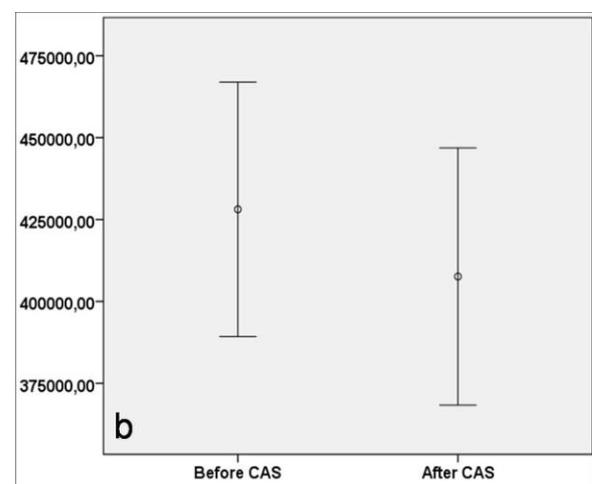
Figure 2. Graphical analyses of pre and post-CAS cerebral volumes: Total cortical white matter volume.
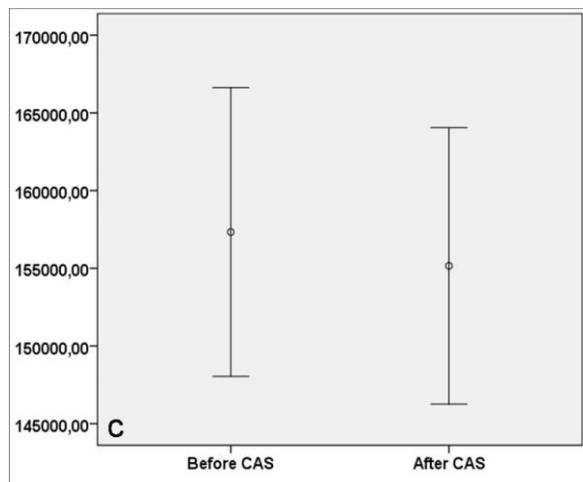
Figure 3. Graphical analyses of pre and post-CAS cerebral volumes: Subcortical grey matter volume.

Figure 4: Graphical analyses of *pre and post-CAS cerebral volumes:* Total intraventricular volume.
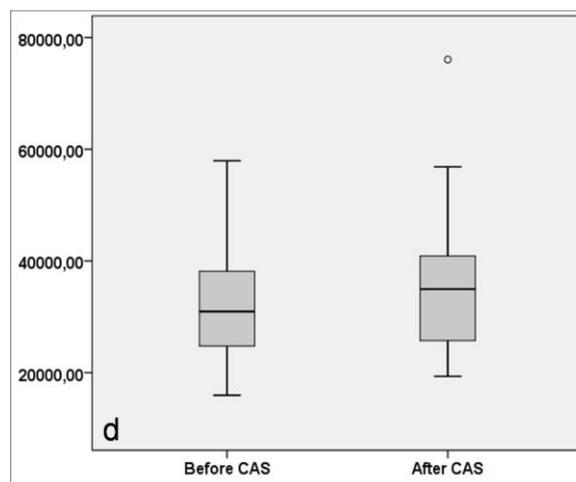
Table 1. Demographic data of 17 patients.

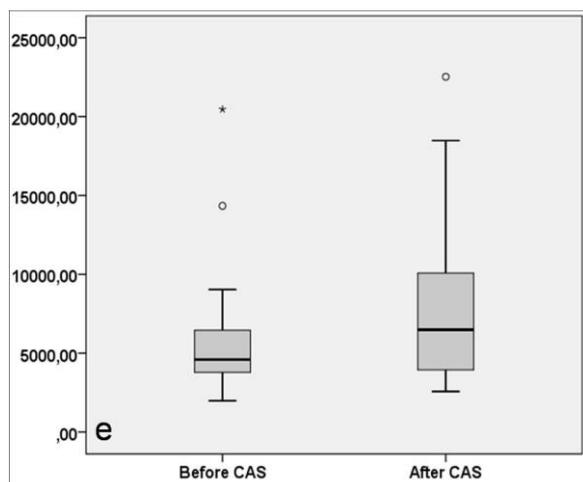| Patients' number	Sex/ age	Carotid stenosis (side and degree (%))	HT	CAD	History of smoking	History of CVE	DM	HL
1	M/69	L: 95	+	+	+	-	-	-
2	F/65	R:95, L:75	+	-	-	-	-	+
3	M/63	L: 90	+	-	+	-	+	-
4	M/71	L: 90	+	-	-	-	-	+
5	M/56	R:75, L: 80	+	-	+	-	-	-
6	M/63	L: 90	+	-	-	+	-	-
7	M/64	R:95	+	-	+	-	-	-
8	M/64	R:95, L: 75	+	+	-	-	+	-
9	M/60	R:95	-	+	+	-	-	-
10	M/61	R:90	+	-	-	+	-	-
11	F/74	R:90, L: 95	+	+	-	-	-	-
12	M/64	L:80	+	+	+	-	-	-
13	M/69	R:80	+	+	-	-	-	-
14	F/77	L: 90	+	+	-	+	-	-
15	M/61	L: 95	+	+	-	-	-	-
16	M/74	L: 90	-	-	+	-	-	-
17	M/63	L:80	+	-	-	-	+	-

M: Male, F: Female, R: Rıght, L: Left, HT: Hypertension, CAD: Coronary Artery Disease, CVE: Cerebrovascular Events, DM: Diabetes Mellitus, HL: Hyperlipidemia

Table 2. Statistical analyses of pre and post-CAS cerebral volumes

Parameters	Before CAS*	After CAS*	p
Total cortical grey matter (mm^3) mean ± sd	381875 ± 41334	381496 ± 41757	0.902
Total cortical white matter (mm^3) mean±sd	428110 ± 75521	412200 ± 73801	0.005
Subcortical grey matter (mm^3) mean ± sd	157333 ± 18077	155154 ± 17297	0.016
Total intraventricular (mm^3) Median (min - max)	30945 (15944 - 57931)	34967 (19333 - 76057)	0.009
White matter hypointensity (mm^3) Median (min - max)	4591 (1980 - 20464)	6491 (2571 - 22526)	0.017

*CAS indicates carotid artery stenting

Figure 5. Graphical analyses of pre and post-CAS cerebral volumes: Total intraventricular volume, (e) White matter hypointensity volume.

DISCUSSION

Magnetic resonance angiography (MRA) and transcranial doppler demonstrated that collateral circulation in patients with ICA stenosis did not played a role in assessment of the brain perfusion. Digital subtraction angiography (DSA) also provided significant information about the collateral circulation. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are invasive methods, whereas arterial spin-labeling (ASL) MRI is a non-invasive method for the assessment of regional cerebral blood flow (CBF) [6]. Van Laar et al [6] observed a 15% increase in post-CAS regional CBF levels in the ipsilateral hemisphere whereas and Ko et al [7] observed a 21% increase when using ASL-MRI and SPECT.

Distal perfusion pressure and CBF are normal when the collateral pathways are sufficient in severe carotid stenosis [8,9]. If the collateral pathways are insufficient and the perfusion pressure distal to the stenosis is reduced, then autoregulatory dilation can keep the CBF at normal levels. When autoregulatory dilation capacity is exceeded, the CBF will be reduced relative to the cerebral rate of oxygen metabolism (CMRO2). In addition, oxygen extraction fraction (OEF) will be increased to maintain the normal CMRO2. This condition is called 'misery perfusion' or 'stage II

hemodynamic failure', and is the most severe stage of hemodynamic impairment [8,10]. Cerebral vascularization and the brain may adapt to the chronic reduction in CBF in areas of the brain with no cerebral infarction through several potential mechanisms. While CBF may increase with the development of collateral ways, CBF can decrease in order to provide the balance of CMRO2. It is suggested that reduced CMRO2 in normal brain areas can cause selective ischemic neuronal loss [8]. Based on this study, we believe that the chronic hypoxia in patients with stenotic ICA leads to ischemic neuronal loss.

Adult human brain accounts for 2% of the total body weight, receives 15% of the total cardiac output and consumes 20% of the inhaled oxygen. The blood flow delivers oxygen and glucose to neurons needed for transmembrane ion transport, electrical activities, synaptic transmission, macromolecular synthesis, intracellular transport and cytoskeletal integrity. A normal CBF rate is 50–60 mL/100 g/min in primates and 100 mL/100 g/min in rats and gerbils. A 50% reduction in CBF can be tolerated. However, a reduction between 25-50% in CBF can lead to ischemic injury due to inhibition of protein synthesis, prevention of the flow of transient potassium and calcium ions, cytotoxic edema and acidosis. This injury may be followed by neuronal apoptosis. A CBF less than 25% leads to rapidly loss of neuron functions whereas a CBF less than 15-20% of normal values leads to irreversible neuronal damage. The brain is quite susceptible to both focal and global ischemia. Unless ischemia is reversed, reperfusion increases the ischemic injury. Excitotoxicity, impaired calcium ion homeostasis, nitric oxide, free radicals, inflammation and apoptosis can be responsible for cerebral ischemia and reperfusion injury. Nitric oxide and free radicals may either do direct damage or cause indirect damage by means of inflammation and apoptosis [11].

Atherosclerotic risk factors like hyperlipidemia, diabetes, hypertension, smoking and aging may induce release of reactive oxygen species from endothelium, vascular smooth muscle cells and adventitial cells which can lead to impair cerebral autoregulation. Hypoxia caused by

cerebral ischemia may affect a number of neurons at different levels. Several factors such as hypoxia and cerebral ischemia are known to induce neuronal apoptosis in the nervous system [12]. Chen et al [13] demonstrated nuclear DNA damage after middle cerebral artery stenosis and reperfusion in rats, which was indicative of neuronal apoptosis. Pulsinelli et al [14] investigated ischemic neuronal damage following transient bilateral forebrain ischemia in a Wistar rat model of four-vessel stenosis. They occluded vertebral arteries permanently and 24 hours later common carotid arteries transiently for 10, 20 and 30 minutes. After 10 minutes of stenosis, ischemic cell changes were observed in cerebral hemispheres of the rats, and after 30 minutes of stenosis early neuronal damage occurred. The authors concluded that neuronal damage progressively advanced with time.

MR image-guided cerebral cortex thickness estimation methods can be categorized into two groups: surface and voxel-based brain analysis methods. Both methods require initial segmentation of grey matter, white matter and cerebrospinal fluid. Laplacian and Registration are voxel-based methods whereas the FreeSurfer is a surface-based method. Surface-based methods are more widely used compared to voxel-based ones due to accessible software packages such as BrainSuite, BrainVISA and FreeSurfer. The FreeSurfer is the most common method employed in clinical trials beyond all surface-based methods [3], because it is easy to use and rapidly developing brain analysis software for the assessment of functional and structural features and connections in the brain. FreeSurfer is a freeware and can be improved with hardware and software platforms. It allows cross-modal intra-subject registration, combined volume and surface cross-subject registration, probabilistic estimation of cytoarchitectonic boundaries, automated tractography and longitudinal analysis. Furthermore, the software can also be used for the assessment of neurological and genetic basis of neuroanatomical disorders, healthy development and aging [4]. Liem et al [15] reported that surface-based metric parameters (cortical thickness, surface area and volume) of the FreeSurfer have high reliability in the assessment of age-related structural alterations in brain regions of healthy elderly individuals. In our study, we preferred the FreeSurfer software since its easy-to-use nature and the accurate and automate image analysis properties.

This study had some limitations. First, the number of patients included in the study was limited. Second, no CEA control group was analyzed. Third, only the FreeSurfer surface-based method was used. Forth, no clinical examination was performed after CAS. Last, this was a retrospective study without a control group.

In conclusions, intracranial neuronal loss in patients treated with CAS for severe ICA stenosis might be due to neuronal damage as determined by FreeSurfer surface-based volumetric measurements. Furthermore, the significant increase in the total intraventricular volume might be related to the reduction in the total white matter volume. Evaluation of this study together with postmortem studies and other brain analysis softwares will be useful.

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