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MAGNETIC RESONANCE IMAGING

Contrast-enhanced ultrasound to predict the risk of microembolization during carotid artery stenting

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Abstract
Objectives Cerebral microembolization, one of the most frequent complications of carotid artery stenting, is associated with an increased risk of peri- and post-procedural stroke and transient ischemic attack and a mid-term risk of neurocognitive decline. A valuable tool to evaluate carotid plaque instability and risk of embolization is contrast-enhanced ultrasound. With this prospective study we sought to determine the correlation between contrast enhancement of the plaque and cerebral microembolization after carotid stent deployment and to evaluate the clinical impact of the neurological injury.
Materials and methods Thirty-five consecutive patients with carotid artery stenosis and indications for endovascular stenting were enrolled. Before the procedure, patients were evaluated with contrast-enhanced ultrasound to define plaque enhancement (signal intensity). All endovascular procedures were performed under cerebral filter protection. Diffusion-weighted magnetic resonance imaging scans to detect microemboli were obtained before and 48 h after the stent deployment. The Ray auditory verbal learning test to assess neurocognitive function was administered before and 1 month after the procedure.
Results Nineteen patients (54 %) developed new cerebral ischemic lesions after carotid artery stenting. Contrast enhancement of the plaque was greater in the patients with post-procedural microembolization than in those without it [maximum signal intensity 26 ± 7.7 vs. 21 ± 5.2, respectively, ($p = 0.039$), mean signal intensity, 20.7 ± 6.1 vs. 16.5 ± 5.3, respectively ($p = 0.048$)]. No correlation was found between neurocognitive test scores and microembolization or plaque enhancement.
Conclusion Contrast enhancement of the carotid plaque is strongly associated with post-procedural microembolization and for this reason it can be considered a reliable tool for an accurate selection of patients undergoing this endovascular treatment. However, the neurocognitive test scores performed in this study are not enough sensible to appreciate the impact of the neurological injury on the day life activities.

Keywords Contrast-enhanced ultrasound · Diffusion-weighted magnetic resonance imaging · Carotid artery stenting · CEUS · CAS · Microembolization

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Background and purpose

Cerebral microembolization, one of the most frequent side effects of carotid artery stenting (CAS), occurs in 10–40 % of cases [1]. It is mainly due to the accidental embolization from the aortic arch or during the crossing of the internal carotid stenosis with the guide wires and catheters or due to the plaque morphology (soft ulcerated plaques are at higher risk) during stent deployment [2]. The clinical impact of neurological injury and cognitive decline after CAS is

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Table 1 Characteristics and cardiovascular risk factors of the study population divided between patients who developed post procedural cerebral ischemic injury (Microembolization+) and those without post-procedural ischemic injury (Microembolization−)

	Total	Microembolization+	Microembolization−	*p* value
Number of patients	35	19 (54 %)	16 (46 %)	
Age	73.2 ± 5	72.8 ± 5.14	73.5 ± 6.4	0.45
Hypertension	27/35 (77 %)	15/19 (78 %)	12/16 (75 %)	0.79
Smoke	12/35 (36 %)	4/19 (21 %)	8/16 (50 %)	0.08
Diabetes	8/35 (23 %)	3/19 (15 %)	5/16 (31 %)	0.31
Dyslipidemia	19/35 (54 %)	12/19 (63 %)	7/16 (43 %)	0.27
Chronic renal failure	3/35 (8 %)	1/19 (5 %)	2/16 (12 %)	0.51
Chronic obstructive pulmunary disease	2/35 (5 %)	2/19 (10 %)	0/16 (0 %)	0.28
Miocardial infarction	8/35 (23 %)	3/19 (16 %)	5/16 (31 %)	0.31
Stroke/TIA before CAS	3/35 (8 %)	2/19 (10 %)	1/16 (6 %)	0.71
Degree of stenosis	77 ± 4.5	77 ± 4.2	76 ± 4.8	0.46
Periferial arteriopaty	15/35 (42 %)	9/19 (47 %)	6/16 (37 %)	0.58
Ischemic lesions before CAS	9/35 (25 %)	4/19 (21 %)	5/16 (31 %)	0.52

still unclear because, in addition to the presence of many potential confounders, neurologic assessment often fails to capture and predict changes in cognitive function [3, 4]. A valuable technique to define plaque enhancement and potential risk of embolization is contrast-enhanced ultrasound (CEUS) [5–8], while diffusion-weighted magnetic resonance imaging (DW-MRI) is a highly reliable imaging method for detecting recent ischemic brain lesions [9]. The aim of this study is to compare plaque enhancement as evaluated by CEUS with new cerebral ischemic lesions after CAS and to define the clinical impact of the neurological injury.

Methods

The prospective study has been approved by an ethic committee and it has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to their inclusion in the study. We enrolled 35 consecutive patients (28 males, 7 females; mean age 73.2 ± 5) treated with CAS for severe carotid artery stenosis. Three patients (8 %) were symptomatic before the procedure [transient ischemic attack (TIA) with left hemiplegia in 2, and dysarthria and transient right arm paresthesia in 1].

Inclusion criteria

Degree of carotid stenosis >70 % according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) or with a peak of systolic velocity >200 cm/s; symptomatic and asymptomatic patients; contraindication to carotid endoarterectomy.

Exclusion criteria

Secondary carotid artery stenting; occlusion of the ipsilateral middle cerebral artery (MCA); cerebral imaging of haemorragic stroke; patients with neurological impairment >15 according to National Institute of Health Stroke Score (NIHSS).

The indications for CAS were: history of neck radiotherapy ($n = 3$); previous neck surgery ($n = 5$); patient's personal choice ($n = 12$); anatomically unfavourable bifurcation ($n = 3$); contralateral vocal cord paralysis ($n = 2$); and medical/anaesthesiological contraindication to open surgery ($n = 10$) (Table 1).

Imaging and cognitive assessment

Preoperative echo-Doppler ultrasound scans (MyLab 25Gold, Esaote®) were obtained to define plaque morphology and measure the degree of stenosis [10], followed by CEUS to evaluate plaque enhancement. Preoperative neurologic assessment included head magnetic resonance (MR) examination (Philips Achieva 1.5 T, head coil) and neuropsychological test [Ray auditory verbal learning test (RAVLT)]. The MR protocol was performed with T1-weighted sagittal, T2-weighted axial, fluid-attenuated inversion recovery (FLAIR) axial and diffusion-weighted imaging (DWI) with quantitive analysis using apparent diffusion coefficient (ADC) maps. Ischemic lesions of the cerebral hemispheres, size, and location were recorded and analyzed by a single operator.

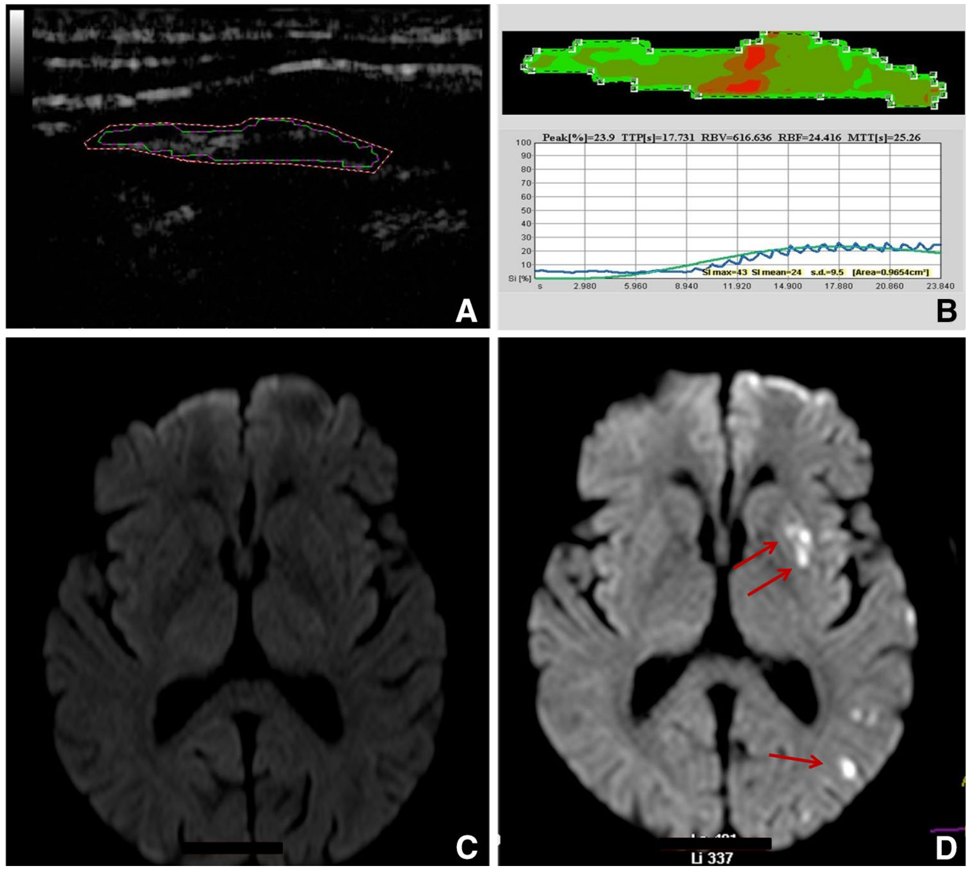

Fig. 1 **a** Contrast enhancement of a carotid vulnerable plaque (*dashed line* region of interest ROI). **b** Analysis of the same plaque with Quontrast® *above* a color map representing in *red* the area of higer enhancement and in *green* the area of lower enhancement, *below* computer assisted evaluation of CEUS pattern with SI max and SI mean calculation. **c**, **d** Comparison between pre- and post-procedural DW-MRI of the same patient showing new microembolization areas (*red arrows*)

CAS procedure

Angiography was performed in local anesthesia after the administration of a load dose of 300 mg clopidogrel, through a percutaneous femoral access; a cerebral protection filter (SpiderFX®, Covidien, Plymouth, MN) was then deployed into the internal carotid downstream the stenosis. CAS was performed with a Bard Vivexx® stent (Bard, New Providence, NJ) in 30 cases, a Carotid Wallstent® (Boston Scientific, Natick, MA) in 3 and an Xact® (Abbott Vascular, Redwood City, CA) in 2. Postprocedural hemostasis was achieved with manual compression. A 1-month course of double antiplatelet therapy [clopidogrel 75 mg and acetylsalicylic acid (ASA) 100 mg] was initiated, followed by lifelong single antiaggregation therapy with ASA.

Postprocedural patient evaluation and follow-up

Before discharge, a second DW-MRI study was performed 48 h after CAS to detect potentially new brain ischemic lesions. Follow-up examination included echo-Doppler ultrasonography (at 1, 6, 12 months, and then yearly thereafter) performed by the same operator and clinical and cognitive evaluation (RAVLT) at 1 month after the procedure.

Data collection and statistical analysis

All data from CEUS, DW-MRI and RAVLT scores were collected blinded of the other results to avoid any confounders. CEUS images were analyzed with Quontrast 4.0® dedicated software (Bracco, Milan, Italy), as described in a previous study [5], and the maximum and mean signal intensity (SI max and SI mean) were calculated. Pre and post procedural DW-MRI images were compared to detect the presence of new ischemic lesions and to define the side (ipsilateral-contralateral), size, location, and number (Fig. 1). Moreover, we determined a cut-off value for SI max and SI mean with Cohen *k* and we confirmed the results with the maximization of the harmonic mean of the data distribution.

Primary end-points of the study are: the correlation between the carotid plaque enhancement (CEUS) with post-procedural cerebral embolization (DW-MRI) and to evaluate the the clinical impact of the neurological ischemic injury (DW-MRI) on the procedural and memory cerebral functions (RAVLT).

Secondary end-points are: the technical success of the procedure, post-procedural neurological complications and the rate of restenosis at 1 year of follow up.

Table 2 Results of the study between patients who developed post procedural cerebral ischemic injury (Microembolization+) and those without post-procedural ischemic injury (Microembolization−)

	Total	Microembolization+	Microembolization−	*p* value
Number of patients	35	19	16	
Technical success of CAS procedure	35 (100 %)	19/19 (100 %)	16/16 (100 %)	–
Neurologic post-procedural complication	2/35 (5 %)	2/19 (10 %)	0/16 (0 %)	0.28
SI max	–	26 ± 7.7	21 ± 5.2	0039*
>26		9	2	0.03*
26		10	14	
SI mean	–	20.7 ± 6.1	16.5 ± 5.3	0048*
>20		10	4	0.2
20		9	12	
1 year restenosis	2/35 (5 %)	1/19 (5 %)	1/16 (6 %)	0.51
RAVLT				
Before CAS		8 ± 4.6	7.4 ± 5.4	
After CAS		8 ± 5.5	7.7 ± 4	
p value		0.53	0.62	

* p value <0.05. Below the SI max and SI mean values we reported the distribution of the study population according to the cut-off estimated for each variable. RAVLT p value was evaluated in the same group before and after CAS

For the statistical analysis, the variables, reported as mean ± standard deviation (SD), were compared with the non-parametric Mann–Whitney test. The categorical variables, reported as counts and percentages with 95 % confidence interval, arranged in row × column contingency tables, were analyzed with the Chi square test (with Yates' correction for 2 × 2) or Fisher's exact test. The risk ratio (RR) was computed with its 95 % confidence interval (CI). Statistical significance was set at $p < 0.05$. For $p > 0.05$, the test power and relative false negative probability were estimated.

Results

The degree of stenosis, measured according to NASCET and as evaluated with echo-Doppler ultrasound, was 77 ± 4.5 %. CAS was technically successful in all patients; no residual stenosis, carotid dissection, elastic recoil or stent fracture was seen on the postprocedural angiography images. DW-MRI revealed silent ischemic brain lesions in nine patients (25 %) before CAS. The postprocedural DW-MRI control scans detected new ipsilateral ischemic lesions (from 1 to 5 lesions) in 19 patients (54 %). Neurologic postprocedural complications arose in two patients (6 %): one case of facial paresthesia which completely regressed before hospital discharge and one case of contralateral brachial weakness and numbness which partially resolved at 6-months and totally regressed at one year follow-up. Comparison of the CEUS images showed a statistical difference in the SI max and SI mean between the patients with and those without microembolization [SI max 26 ± 7.7 vs. 21 ± 5.2, respectively ($p = 0.039$), SI mean 20.7 ± 6.1 vs. 16.5 ± 5.3, ($p = 0.048$), respectively]. Afterwards we performed the ROC curve for SI max and SI mean with an area under the curve (AUC) of 0.72 (0.55–0.88) and 0.67 (0.49–0.85), respectively. Results revealed a SI max cut-off value of 26 and SI mean cut-off value of 20. In particular for SI max we found a statistical difference between the patients with values above 26 compared to those with values below the cut off with an increased risk of microembolization of 81 % ($p = 0.03$). The difference for SI mean values was not statistically significant ($p = 0.2$) (Table 2).

At 30 days, follow up with echo-Doppler ultrasound, we found two patients (5 %) with a moderate degree of intrastent restenosis that remained stable at 6 months and 1 year control. There was no statistically significant variation of RAVLT scores for the patients with post-procedural microembolization (8 ± 4.6 before CAS vs. 8 ± 5.5 after CAS; $p = 0.53$) or for those without it (7.4 ± 5.4 before CAS vs. 7.7 ± 4 after CAS; $p = 0.62$).

Discussion

There is a growing body of evidence that CEUS evaluation of carotid artery lesions can be a cost-effective and reliable method to define plaque vulnerability and predict the risk of embolization [5, 6, 11]. Because of the significantly higher risk of periprocedural embolization during primary CAS as compared with carotid endoarterectomy, CEUS can be advantageously applied as a useful imaging system for the assessment of plaque morphology [12]. Stent deployment exerts strong radial forces on arterial walls, augmenting the risk of plaque fragmentation and cerebral embolization. Unfortunately, even the systematic use of cerebral protection filters appears to be insufficient to prevent this complication [13]. DW-MRI is a highly sensitive method for the early detection of ischemic brain regions by virtue of its ability to identify cytotoxic edema, one of the first hallmarks of brain injury [9]. Data from the literature suggest that, as compared with traditional carotid endarterectomy, postprocedural microembolization is associated with faster neurocognitive decline particularly in memory function [3, 4]. Therefore, we compared neuropsychological RAVLT score before CAS and at 1-month follow-up.

We found a direct association between plaque enhancement and postprocedural microembolization, which is consistent with our previous findings on plaque vulnerability and with published data [5, 6]. In detail, patients with a SI max value of more than 26 have a significantly higher risk of developing cerebral microembolization with CAS. The cut-off values of SI mean do not reach statistical significance ($p = 0.2$) however the distribution of values reveal a trend towards a difference between the two groups and this result might be attributable to the small population size.

We found no correlation between CEUS results and the number of the cerebral lesions or a significant difference between the number of lesions and clinically relevant neurological symptoms. This could be partially explained by the presence of silent parenchymal brain regions or hemodynamic mechanisms of brain compensation ("washout" phenomenon) [14, 15]. The RAVLT scores failed to reveal a decline in memory function in patients with microembolization at 1 month follow-up. This finding contrasts with previous observations [3, 4] and is partially attributable to the specific neurocognitive domain investigated, and patient compliance. To the best of our knowledge, this is the first study that directly compares CEUS evaluation of the carotid plaque with CAS post-procedural microembolization. Despite the relatively small sample size, our data are supported by a high statistical significance. As this is an ongoing study, it is important to confirm these results on a larger population study and to investigate other neurocognitive domains with multiple tests and for a longer follow-up.

Conclusion

Contrast enhancement of the atherosclerotic plaque is strongly associated with the risk of microembolization after carotid stenting deployment. For this reason CEUS could become a mandatory assessment to select patients who benefit most from CAS. Further neurological tests are recommended to appreciate the clinical impact of the cerebral ischemic damage after the procedure.

Conflict of interest None.

Ethical standards This article does not contain any studies with human participants or animalsperformed by any of the authors.

References

1. Maggio P, Altamusa C, Landi D, Migliore S, Lupoi D, Moffa F et al (2013) Diffusion weighted lesions after carotid artery stenting are associated with cognitive impairment. J Neurol Sci 328:58–63
2. Yamada R, Anderson MB, Guimaraes M, Schönholz C (2013) Carotid stenting in asymptomatic patients: how to identify patients without symptoms and at high risk for neurologic events. J Cardiovasc Surg 54:55–59
3. Capoccia L, Speziale F, Gazzetti M, Mariani P, Rizzo A, Mansour W et al (2010) Comparative study on carotid revascularization (endoarterectomy vs stenting) using markers of cellular brain injury, neuropsychometric tests, and diffusion-weighted magnetic resonance imaging. J Vasc Surg 51:584–592
4. Zhou W, Hitchner E, Gillis K, Sun L, Floyd R, Lane B et al (2012) Prospective neurocognitive evaluation of patients undergoing carotid interventions. J Vasc Surg 56(6):1571–1578
5. Varetto G, Gibello L, Bergamasco L, Sapino A, Castellano I, Garneri P et al (2012) Contrast enhanced ultrasound in atherosclerotic carotid artery disease. Int Angiol 31(6):565–571
6. Ten Kate GL, van den Oord SC, Sijbrands EJ, van der Lugt A, de Jong N, Bosch JG et al (2013) Current status and future developments of contrast-enhanced ultrasound of carotid atherosclerosis. J Vasc Surg 57(2):539–546
7. Clevert DA, Paprottka P, Sommer WH, Helck A, Reiser MF, Zengel P (2013) The role of contrast-enhanced ultrasound in imaging carotid arterial diseases. Semin Ultrasound CT MR 34:204–212
8. Ritter MA, Theismann K, Schmiedel M, Ringelstein BE, Dittrich R (2013) Vascularization of carotid plaque in recently symptomatic patients is associated with the occurrence of transcranial microembolic signals. Eur J Neurol 20:1218–1221
9. Bijuklic K, Wandler A, Varnakov Y, Tuebler T, Schofer J (2013) Risk factors for cerebral embolization after carotid artery stenting with embolic protection: a diffusion-weighted magnetic resonance imaging study in 837 consecutive patients. Circ Cardiovasc Interv 6(3):311–316
10. Antignani PL, Benedetti-Valentini F, Aluigi L, Baroncelli TA, Camporese G, Failla G et al (2012) Diagnosis of vascular diseases. Ultrasound investigations—guidelines. Int Angiol 31:1–77
11. Mauri G, Porazzi E, Cova L, Restelli U, Tondolo T, Bonfanti M et al (2014) Intraprocedural contrast-enhanced ultrasound (CEUS) in liver percutaneous radiofrequency ablation: clinical impact and health technology assessment. Insights Imaging 5(2):209–216
12. Liu ZJ, Fu WG, Guo ZY, Shen LG, Shi ZY, Li HJ (2012) Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. Ann Vasc Surg 26(4):576–590
13. Brewster LP, Beaulieu R, Corriere MA, Veeraswamy R, Niazi KA, Robertson G et al (2011) Carotid revascularization outcome

comparing distal filters, flow reversal, and endoarterectomy. J Vasc Surg 54:1000–1004

14. Zhu L, Wintermark M, Saloner D, Fandel M, Pan XM, Rapp JH (2011) The distribution and size of ischemic lesions after carotid artery angioplasty and stenting: evidence for microembolization to terminal arteries. J Vasc Surg 53:971–976
15. Schreiber S, Serdaroglu M, Schreiber F, Skalij M, Heinze HJ, Goertler M (2009) Simultaneous occurrence and interaction of hypoperfusion and embolism in a patient with severe middle cerebral artery stenosis. Stroke 40:478–480