Optimizing care for patients with symptomatic carotid disease
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ABSTRACT

Background. Vulnerability of the carotid plaque might be useful as a predictor for ischemic stroke risk. The Gray-Scale Median (GSM) of the carotid plaque at B-mode imaging has been described as an objective tool to quantify vulnerability. However, its’ use is disputed in the literature. This study aimed to validate the GSM as a predictor for carotid plaque vulnerability.

Methods. We included eighty-nine consecutive patients (mean age 68 ± 1 years, 64 males) who were evaluated for carotid endarterectomy. The GSM was derived from preoperative B-mode images and related to the presence of clinical symptoms, the presence of ipsilateral infarction on neuroimaging and to the number of intraoperative ipsilateral micro-emboli (ME) detected by transcranial doppler. Furthermore, we combined the GSM with its standard deviation (GSM-SD), which we hypothesized to be a measure for plaque heterogeneity and thereby vulnerability.

Results. B-mode imaging showed a wide variety in GSM amongst all plaques (median 36, range 6-89). No relation was found between the GSM and any clinical, radiological or intra- and postoperative neurological phenomena. These data showed no additional value of the use of GSM in evaluating plaque vulnerability.

Conclusions. No relation was found between the GSM and any clinical, radiological or intra- and postoperative neurological phenomena. These data showed no additional value of the use of GSM in evaluating plaque vulnerability.

INTRODUCTION

Large randomized trials in the 1990s demonstrated that carotid endarterectomy (CEA) is beneficial with respect to the long-term reduction of stroke risk in symptomatic patients with severe stenosis (70-99%) of the internal carotid artery (ICA). Since then, the degree of carotid stenosis is the key-stone in decision-making whether or not to perform CEA. However, in the ECST study only 32% of all symptomatic patients actually had a stenosis of 70-99%. Furthermore, numbers needed to treat seem to be high with increased risk for morbidity in large numbers of patients without any long-term benefit, especially in those with moderate and/or asymptomatic stenosis.

Other plaque characteristics besides degree of stenosis might have an additional value in identifying more accurately those patients with the highest risk for stroke. Recently, vulnerability of the carotid plaque has gained more attention as a possible predictor for stroke risk. Histological studies have shown clear differences between symptomatic and asymptomatic plaques. In symptomatic plaques, the fibrous cap is thinner and inflammation is more common, with greater numbers of macrophages and T-cells. In addition, symptomatic plaques have a larger lipid-rich necrotic core and lower degree of calcification than asymptomatic plaques. Detection of these characteristics might identify those patients with an increased risk for stroke more thoroughly. B-mode ultrasound imaging can identify certain plaque characteristics found in symptomatic plaques. The Gray-Scale Median (GSM) of B-mode ultrasound images has been suggested as a possible tool to quantify plaque vulnerability. The GSM is a computer-assisted grading of the echogenicity of atherosclerotic plaques. It is a measure of overall plaque echogenicity, which is a quantitative index of the echoes from the plaque. However, the use of the GSM as predictor for carotid plaque vulnerability has been disputed in the literature. Since the GSM is an overall measure of plaque echogenicity, a plaque can still have ‘neutral’ GSM values despite highly echolucent areas (prone for rupture) due to counterbalancing echogenic areas. The standard deviation of the mean pixel distribution (GSM-SD) might have an additional value to the GSM as a measure of heterogeneity. A plaque with a high GSM and a low standard deviation would indicate a stable plaque. However, a high standard deviation accompanying the same GSM value might detect an echolucent (unstable) area in an overall echogenic plaque.

We therefore analyzed data from a prospective single-center database registry in order to see whether we could validate the GSM and the GSM-SD as a predictor for carotid plaque vulnerability by relating the GSM to clinical presentation, infarction on cerebral imaging and intraoperative micro embolic signals (MES) on transcranial Doppler (TCD).

METHODS

Patients

All consecutive patients from a prospective single-center database registry, containing patients who underwent CEA between January 1st 2008 and December 31st 2009, were enrolled. General inclusion criteria for CEA at our institution were symptomatic patients (e.g. amaurosis fugax (AF), transient ischemic attack (TIA) and ischemic stroke) with a ≥ 70 % carotid stenosis, and asymptomatic patients...
with a ≥ 80% carotid stenosis, as defined with duplex ultrasound. All patients were initially referred by a neurologist by whom the clinical presentation was evaluated. On indication additional imaging (computerized tomographic angiography (CTA-scan) or magnetic resonance angiography (MRA)) was performed. Both CTA and MRA imaging were judged by a radiologist.

**Duplex and Gray-Scale Median**

After referral, all carotid arteries were investigated by one experienced certified vascular laboratory technician. Duplex ultrasound (SONOLINE Antares Ultrasound Imaging System; Siemens Medical Solutions, Issaquah, WA, USA) was performed with the aid of a VFX9-4 Multid linear array transducer. The degree of stenosis was based on the measured velocities and estimated using thresholds according to Bluth et al., or in case of asymptomatic stenosis, thresholds derived from the criteria of Moneta et al. were applied.12,13

B-mode images of the carotid plaques were transferred to a personal computer and standardized using Adobe Photoshop 7.0 (Adobe Systems Inc, San Jose, CA, USA). For this, an area in the blood was selected as reference structure for hypoechogenicity and a part of the adventitia was selected as a reference structure for hyperechogenicity. Then, linear scaling was performed using Adobe Photoshop so that the lumen had a GSM of 5 and the adventitia a GSM of 195.14 Subsequently, the carotid plaque was outlined in the standardized image and the GSM, including standard deviation (GSM-SD), were measured using the histogram facility in the software. Color Doppler images were used to assist in outlining the hypoechogenic plaques. The exact method of standardization and measuring the GSM using Adobe Photoshop has been described in detail previously.15,16 Standardization of all images and measurements of the GSM of all carotid plaques in our study were performed by the same experienced vascular technician.

**Surgical procedure**

All CEAs were performed under general anesthesia with EEG and TCD monitoring using standard surgical techniques by certified vascular surgeons in our tertiary referral hospital.17

**TCD Monitoring**

Continuous TCD monitoring (Nicolet Companion III17; Nicolet Vascular, Madison, WI, USA) was applied throughout surgery with the ipsilateral middle cerebral artery insonated at a depth between 5.0 and 6.0 cm using a 1.6-MHz monitoring probe with a diameter of 2 cm. An intensity detection threshold of ≥ 8 dB was chosen to discriminate micro-embolic signals from the background scatter. Scale settings were optimized for each patient. Further settings were as follows: a sample volume of 8 mm, a 256-point FFT and a high-pass filter of 150 Hz.

All embolic signals 30 minutes prior to clamping were analyzed and counted manually after surgery by one investigator and used in this study. We deliberately chose this 30 minutes period before clamping to avoid inadvertently capturing any signals produced by air emboli or remaining debris due to traumatic clamping or the endarterectomy itself.

**Statistical Analysis**

Statistical analysis was performed using the Statistical Package for Social Sciences 16.0 (SPSS Inc, Chicago, IL, USA). The reliability of outlining the plaque perimeter by computer mouse for GSM measurements by the vascular laboratory technician was assessed by calculating the intraclass correlation. The median was used to differentiate between patients with a high and low GSM and high and low GSM-SD. Analysis of variance was used to study the relationship between risk factors and GSM (univariate analysis), as well as the association of the GSM with clinical presentation (ANOVA). Student's t-test was used for comparison of the mean GSM of patients with and without preoperative radiological abnormalities. Bivariate correlation coefficient was used to determine a relationship between GSM and micro-emboli.
Comparisons between clinical presentations in different subgroups (low GSM with low GSM-SD versus high GSM with low GSM-SD) were performed by means of the Chi-Square test. Throughout the analyses \( p < 0.05 \) (two-tailed tested) was considered to be statistically significant. Results are presented as the mean ± standard deviation.

RESULTS

A total of 96 patients underwent elective CEA during the defined period. Seven patients (7%) were excluded because the GSM was analyzed in another hospital or vascular laboratory. Of the remaining 89 patients, 12 were asymptomatic, 18 underwent surgery because of AF, 27 because of a TIA and 32 had suffered a minor stroke. Patient characteristics and frequencies are shown in table 1. Post-operatively, four patients (4%) suffered from TIA and two patients (2%) from stroke. Mean hospital stay was four days (range 2 - 87), mean follow up 17 months (range 0 - 41).

Intraclass correlation of the GSM measurements by the technician was found to be good (intraclass coefficient 0.80). Univariate analysis showed no significant association between sex \( (p=0.98) \), age \( (p=0.48) \), current smoking \( (p=0.53) \), hypertension \( (p=0.42) \), hyperlipidemia \( (p=0.46) \), obesity \( (p=0.83) \) or diabetes mellitus \( (p=0.91) \) and the GSM.

The mean GSM-value of asymptomatic patients did not differ from those in which symptoms had been present \( (37.8 ± 8.9 \text{ versus } 37.6 ± 17.1; p=0.97) \). After stratifying the value of GSM by quartiles \( (0-26, 26-36, 36-47 \text{ and } 47-89) \), we neither could find a relation between GSM and symptoms or not, comparing patients with a GSM of 0-26 and patients with a GSM of 47-89 \( (\text{Fisher exact; } p=0.61) \). Also no significant difference in GSM-value was found between asymptomatic patients and symptomatic patients distinguished by neurological presentation \( (37.8 ± 8.9 \text{ versus } 44.8 ± 19.9 \text{ (AF), } 37.7 ± 19.1 \text{ (TIA), } 33.6 ± 12.2 \text{ (stroke); } p=0.18; \text{figure 1}) \).

Pre-operative imaging was performed in 70 patients (89%). Four of these patients were asymptomatic (three of them presented with tinnitus, one had aphasia more than 18 months before), eight patients presented with AF, 26 with a TIA and 32 had suffered a stroke. Pre-operative imaging showed ipsilateral ischemic lesions in 30 cases. In patients with ipsilateral ischemic lesions on pre-operative CTA-scan or MRA, the mean GSM-value was 36.0 ± 14.6 compared to 37.8 ± 16.9 in patients without ischemic lesions \( (p=0.64; \text{figure 2}) \).

Bivariate correlation analysis showed no significant correlation between the GSM-value and number of intra-operative micro-embolic signals 30 minutes before clamping \( (\text{Spearman correlation, } n=73, \rho=0.039, p=0.75; \text{figure 3}) \).

The mean GSM of patients who postoperatively suffered from neurologic complications (TIA n=4; major stroke n=2) was 39.5 (± 12.8) compared to 37.5 (± 16.5) in patients without postoperative neurological complications.

Combining the GSM with its SD could not indicate a specific group of patients having a more vulnerable carotid plaque. The median GSM-value after analyzing B-mode images of all plaques was found to be 36 (range: 6 – 89). The median SD of plaques with a GSM ≤ 36 (n=46) was 30.7, of those with a GSM > 36 (n=43) was 40.0. Comparing event rates of patients with presumably the most vulnerable plaques (low GSM, low GSM-SD; n=25) with those of patients with presumably the most stable plaques (high GSM, low GSM-SD; n=20) did not demonstrate any significant difference \( (\text{Chi-square test, } p=0.56, p=0.80 \text{ and } p=0.77 \text{ for symptomatology, ipsilateral detectable infarction on neuroimaging, and numbers of intraoperative embolic signals on TCD respectively}) \).

Figure 1. Gray-scale median, grouped by symptomatology. The dark lines in the middle of the boxes are the median GSMs. The T-bars represent the minimum and maximum values. The mean GSM is provided in the upper text box above the boxes, the number of patients in the lower text box.

Figure 2. Gray-scale median in patients with and without detectable ipsilateral infarction on preoperative neuroimaging. The dark lines in the middle of the boxes are the median GSMs. The T-bars represent the minimum and maximum values. The mean GSM is provided in the upper text box above the boxes, the number of patients in the lower text box. The open dot seen above the left box is an outlier (GSM 89).
Chapter 5

Relation between B-mode gray-scale median and clinical features of carotid stenosis vulnerability

DISCUSSION

This study data showed no relationship between objective neurological events and the GSM score of carotid plaques on B-mode imaging. Furthermore, comparing patients with the theoretically most vulnerable plaques to those in patients with the theoretically most stable plaques did neither demonstrate any significant difference in event rate. These results do therefore not provide any additional value of the GSM in evaluation of plaque vulnerability and with that, in evaluation of ischemic stroke risk in patients with carotid stenosis.

This is in contrast to other studies, in which echolucent plaques have been shown to have an increased risk of ischemic cerebrovascular events. In the Tromsø study, patients with echolucent atherosclerotic plaques had an increased risk of ischemic cerebrovascular events, independent of degree of stenosis and cardiovascular risk factors. However, echolucency was classified according the Gray-Weale classification, which is more prone to subjectivity than the GSM. Sabetai et al used the GSM as measure of echolucency and found an evident association between the GSM and hemispheric symptoms. Their study was, although it had a higher number of patients, quite comparable to ours.

The international multicenter ICAROS registry also showed an increase in stroke risk in carotid artery stenting (CAS) in patients with a GSM ≥ 25. However, Reiter et al could not identify patients with an increased risk for neurological events after CAS by using the GSM. Moreover, it is questionable if results of studies in which carotid plaques are exposed to crossing guide wires and in which debris might detach from plaques during stenting can be extrapolated to the patients undergoing carotid endarterectomy. Perhaps more relevantly, can those results be used to distinguish a vulnerable plaque from a stable one in asymptomatic patients? After all, all symptomatic patients were once asymptomatic.

Cerebral infarction on neuroimaging in patients with carotid disease indicates that there has been plaque rupture with distal embolisation. Thus, if echolucency is associated with the vulnerable carotid plaque, one might also expect an association between echolucency of the plaque and cerebral infarction on neuroimaging. Previous studies have indeed associated echolucent plaques with a higher incidence of cerebral infarction on neuroimaging. We were however unable to demonstrate a similar association.

Manipulation of the vessel during dissection might evoke micro embolic events from the carotid artery plaque. Theoretically, this would be more explicit in vulnerable plaques and thus in echolucent plaques. However, we did not find any association between GSM and MES on intraoperative TCD. Telman et al could neither find a correlation between the density of plaques (using the GSM) and the number of MES on intraoperative TCD. Madycki et al did however show that a refined analysis of plaque texture can predict the number of intraoperative MES, but standard GSM was also in their study not associated with the rate of MES. Conversely, a cross-sectional study by Tegos et al to determine the association between embolic signals detected by TCD and, amongst other things, ultrasonic tissue characteristics of carotid plaques, did show an inverse relation between the GSM and the number of embolic counts.

An earlier publication by the same group on echomorphologic and histopathologic characteristics of unstable carotid plaques, demonstrated that the GSM was unrelated to the relative necrotic core size and was also unable to distinguish the calcified from the non-calcified plaques, although it could separate the hemorrhagic from the non-hemorrhagic ones. In contrast, El-Barghouty et al showed that plaque computer echogenicity measurement in the form of the gray-scale median correlated well with histology. These last studies indicate that validation of the GSM as predictor for plaque stability by plaque histology is also weak.

Recent literature is clearly ambiguous regarding the value of the GSM as an objective tool for echolucency and, with that, the identification of plaque instability. Our study puts further question marks on the use of the GSM as a predictor for stroke risk in patients with carotid stenosis.

One of the limitations of the GSM is that it is a median value of pixel brightness of the entire carotid plaques, leaving focal variability out of consideration. The GSM of a homogenic gray field and the GSM of a “check board” will theoretically be equal, although the pattern is totally different. Although such a plaque has a normal GSM value, rupture could theoretically take place in an echolucent part of the plaque. Lal et al have therefore described a refined method to analyze pixel distribution of carotid plaques. This method however comprehends an additional imaging program. In our study, we combined the GSM with its standard deviation (GSM-SD), of which one may also expect to be a measure for the heterogeneity, and which is provided by Adobe Photoshop as is the GSM value itself. A plaque with a low GSM and a low GSM-SD would theoretically mainly consist of hemorrhage and/or lipid and thus be more vulnerable. A plaque with a high GSM and low GSM-SD would theoretically be more calcified and contain more fibrin, and therefore be more stable. However, our results could not support this hypothesis.

Another limitation in the use of the GSM is the subjectivity in outlining the plaques before GSM analysis is performed, although studies have shown a reasonable intra- and interobserver variability. In our study, we have restricted this limitation by performing the analysis by 1 experienced vascular technician. Outlining the plaque perimeter seemed reliable.
GSM might thus not be the proper tool for detecting those patients with carotid plaque instability. Other currently available clinical imaging methods (CT-A and MRA) cannot produce definite information about plaque instability either. Various new advanced imaging methods, such as single photon emission computed tomography (SPECT), positron emission tomography (PET) and near-infrared fluorescence (NIRF) are available nowadays. These nuclear imaging modalities are capable of visualizing metabolic activity and molecular processes using radionuclide and fluorescent tracers that identify inflammation, apoptosis and proteolysis, which are highly related with plaque vulnerability. However, further research is needed before there will be clinical applicability.

The results of our study are limited by its retrospective character, which also leads to selection bias, as all patients included were already under evaluation for surgery. However, since the asymptomatic patients with higher grades of stenosis we operate on in our hospital have theoretically more stable plaques, they can function as a justifiable control group in our opinion.

In conclusion, standard GSM-analysis alone, or in combination with its standard deviation as a measure for heterogeneity, could not be related to symptomatology, detectable lesions on brain imaging or intraoperative MES. It therefore cannot be used to distinct true asymptomatic from potential symptomatic plaques and thus cannot indicate those patients who would best benefit from CEA. Since previous publications on this topic are ambiguous as well, further studies should focus on other ways of identification of vulnerable plaques.

REFERENCES

Chapter 5

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