Identification of Vascularised Carotid Plaques Using a Standardised and Reproducible Technique to Measure Ultrasound Contrast Uptake

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Objectives: Contrast-enhanced ultrasonography (CEUS) has been used to assess the vascularisation of carotid plaques. Our aim was to develop and validate a standardised semi-automated method for CEUS examination of plaques, and test if the technique could be used to identify vulnerable plaques.
Methods: Study participants were a mixed population of symptomatic and asymptomatic subjects, selected if they had a plaque with height >2.5 mm and <10% acoustic shadowing. Participants received a bolus of ultrasound contrast agent and a 90-s cine-loop was captured. A Contrast Quantification Program (CQP) was developed and trained to identify extent of contrast uptake after motion correction and application of a noise reduction algorithm. The technique was validated by comparing CQP values with visual assessment of contrast uptake. CQP values were also compared with plaque echogenicity and history of clinical events.
Results: CQP values correlated with a visual, 5-scale classification of contrast uptake by two blinded, experienced sonographers. Repeated contrast injections showed high reproducibility. Participants with a history of ipsilateral stroke/TIA had significantly higher CQP values than asymptomatic participants.
Conclusion: We present a reproducible, semi-automatic method to identify vascularisation of carotid plaques, which could be used in prospective studies to determine the clinical value of plaque vascularisation.

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INTRODUCTION

Intense efforts have been devoted to developing imaging techniques for identification of vulnerable atherosclerotic plaques prone to cause clinical events.[1,2] It is generally considered that a large lipid-rich necrotic core and a dense infiltration of inflammatory cells, particularly in the shoulder regions, predicts vulnerability while a thick fibrotic cap is associated with a more stable plaque phenotype.[2,3] However, most evidence to support this concept is based on autopsy and cross-sectional histological studies.[3] Magnetic resonance imaging (MRI) of human carotid plaques has evolved as a promising technique to identify and quantify these different plaque phenotypes,[2,4] but it is too expensive to use as a diagnostic tool on a large scale. In addition, the grey scale of ultrasound can be used to differentiate lipid-rich carotid plaques with low echogenicity from more fibrous tissue with higher echogenicity.[2,5,6]

Recent evidence suggests additional features that are central in determining the vulnerability of plaques, namely intra-plaque vascularisation and intra-plaque haemorrhage (IPH).[1,7] IPH likely results from bleeding from immature vessels formed after vascular proliferation.[7] Increased vascularisation has been observed in histological sections of symptomatic plaques.[8] In addition, a large histological study of carotid endarterectomy specimens showed that IPH was the aspect of plaque histology that most readily predicted future cardiovascular events, superior to lipid content and degree of inflammation.[9] Furthermore, IPH detected by MRI has been shown to predict future ipsilateral stroke.[10,11]

Contrast-enhanced carotid ultrasonography (CEUS) has been used to measure plaque vascularisation in vivo in humans,[12–18] and several studies have shown a good to excellent correlation between visual assessment of ultrasound-assessed contrast uptake in the plaque and the vascularisation of corresponding histological sections.[12,14,15] However, visual assessment is highly user dependent and difficult to use as a diagnostic tool and in research. Here we developed and validated a standardised reproducible and semi-automated method for CEUS examinations of carotid plaques. In addition, we investigated how contrast enhancement measured with our semi-automated method correlated with plaque echogenicity measured using standard ultrasound imaging as well as with previous clinical events.

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MATERIAL AND METHODS

Study population

The subjects consisted of patients selected from the Western region Initiative to Gather Information on Atherosclerosis (WINGA) database, which includes patients at Sahlgrenska University Hospital undergoing ultrasound examination for suspected cerebrovascular disease, and healthy volunteers aged 68–73 years identified through official registers and invited to screening for carotid artery atherosclerosis.

Inclusion criteria were at least one carotid plaque with minimum height 2.5 mm and an acceptable acoustic window where <10% of the plaque surface had ultrasound acoustic shadowing. Exclusion criteria were: age >80 years; history of myocardial infarction; cardiac surgery or percutaneous coronary interventions within the previous 6 months; angina pectoris; right to left heart shunts; severe arrhythmias; pulmonary hypertension; uncontrolled systemic hypertension (>180/110 mmHg); heart failure with symptoms in NYHA class III-IV; advanced chronic obstructive pulmonary disease; multiple transient ischaemic attacks (TIA) within the previous 2 weeks; unable to communicate in written and spoken Swedish.

The study conforms to the Declaration of Helsinki and has been approved by the ethics committee at Sahlgrenska Academy, Gothenburg University. All subjects gave written, informed consent.

Baseline characteristics

Subjects were invited to the laboratory and detailed clinical and life style data were collected using a standardised questionnaire. Data on anthropometry, blood pressure and ECG were collected and venous blood samples were drawn as previously described.[19]

Image acquisition

Subjects were imaged using a Siemens S2000, update VA16D, ultrasound platform (Siemens, Mountain View, California, USA) equipped with a 9L4 probe used at 9 MHz for standard imaging and 4 MHz for cadence imaging. A longitudinal transducer position was chosen to show an image-plane perpendicular through the centre of the vessel and through the maximum height of the plaque. The full length of the carotid arteries were scanned, and short, B-mode cine loops of all plaques fulfilling the inclusion criteria were stored digitally.

Cadence contrast pulse sequencing (CPS) technology for Siemens S2000 was used to image contrast uptake in the plaques identified by B-mode imaging. We performed a separate series of 15 pilot experiments to optimise the settings for the cadence CPS and the dose of contrast agent (Sonovue, Bracco Imaging, Milan, Italy). These experiments also showed that the critical minimum height of the plaque should be 2.5 mm. The protocol was then fixed and not altered throughout the examinations presented in this paper.

The standardised image settings included a low mechanical index (0.06) and a low overall 2D-gain focusing on the contrast agent and making the tissue less prominent. In the pilot experiments we found that an MI of 0.06 was the optimal setting that could be used without losing image information. The CPS image without contrast in the lumen should be almost completely black. The contrast agent was injected as a bolus (1.6 ml) in a peripheral vein and flushed with 10 ml of saline according to the manufacturer's instructions (Bracco Imaging, Milan, Italy). The sonographer aimed at imaging the plaque at a fixed insonation angle and a DICOM cine loop was recorded for 150 s starting when the contrast bolus was injected. Each subject received 2 or 3 bolus injections, each separated by a 30-min washout period.

Analysis of B-mode images

For the images obtained using standard B-mode ultrasound (Fig. 1A), plaque size was measured and echogenicity was assessed using the visual Gray-Weale scale and the automated Grey Scale Median (GSM) and Percentage White (PW) scale using semi-automated software.[20]

Analysis of CEUS images by Contrast Quantification Program (CQP)

All handling and analyses of CEUS images were integrated in CQP, our development software platform. The 150-s contrast loop was stored in DICOM format at 24 or 26 frames per second and each frame was later converted into bitmap files. The first image frame showing contrast in the arterial lumen was identified and set as the starting frame (Fig. 1B). The series of frames was resampled from the starting frame extracting one frame per second for 90 s.

CQP was developed to analyse contrast uptake in the image loop in a series of standardised steps:

(1) The plaque border was manually outlined using a region of interest (ROI) on a frame in which the vessel lumen was filled with contrast (Fig. 1C).
(2) All images in the series were manually motion corrected using the fixed ROI, which could be moved and tilted.
(3) In every frame, the mean pixel intensity in a reference area, placed in the carotid lumen close to the plaque (Fig. 1B), was calculated. The highest and lowest values of mean intensity during the series of frames were used as white and black references, respectively. In all frames, a linear normalisation was performed where the black reference pixel intensity value was set to 10 and the white reference pixel intensity value was set to 200.
(4) If the image plane was lost for a short period (for example, if the subject swallowed) and the image plane was then restored by the technician, the affected frames were excluded and given a value interpolated as the mean of the values from the adjacent frames.

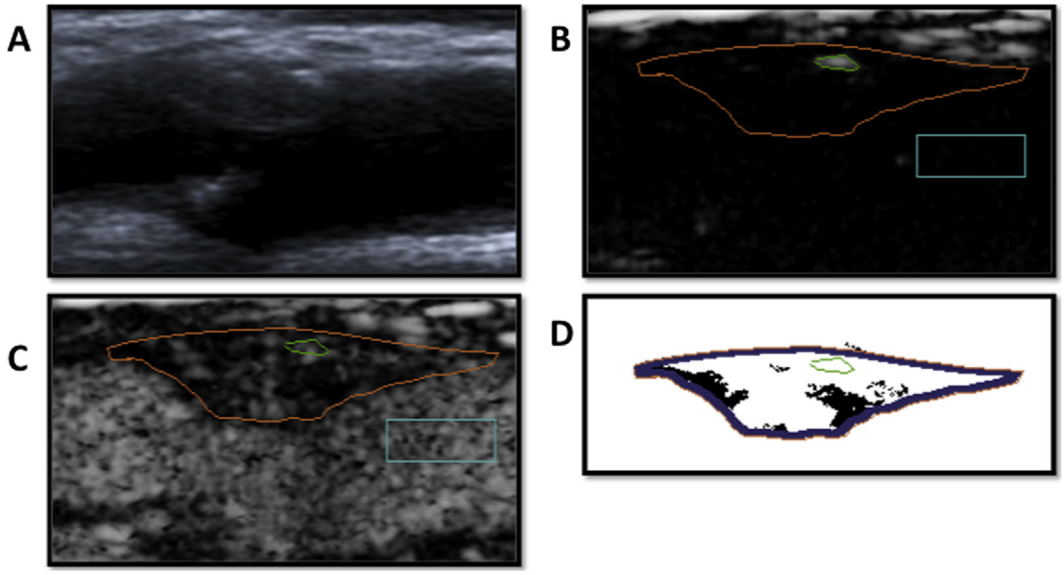

Figure 1. A: B-mode image of plaque with low echogenicity in the near wall of the internal carotid artery/bulb. B: Screenshot from CQP software when first contrast bubble arrives in vessel lumen. Note artefact area marked green. C: Screenshot from the CQP software. Plaque borders marked orange; intensity reference area marked blue; manually excluded area marked green. D: Processed image from CQP. White area inside plaque border indicates contrast containing area. 81% of plaque area is contrast containing.

(5) A noise reduction and contrast detection algorithm was developed. A pixel was considered contrast positive if the intensity exceeded 35 (the noise threshold), for at least 14% of the time.
(6) To compensate for inexact motion correction, a border of four pixels (0.25 mm) was subtracted from the plaque ROI.
(7) The percentage of pixels in the plaque with a contrast intensity exceeding those set by the time-intensity algorithm during the 90-s loop was calculated and used as an index of contrast uptake; this was termed "CQP value."

Training and validation of CQP

Training and validation of the CQP followed standard guidelines for development of pattern recognition software.[21] The CQP was trained on 10 plaques from 10 subjects showing a range of contrast uptake from zero to maximum intensity. The CPS DICOM loops were converted to AVI files and visually classified by two experienced sonographers (UP and CS) blinded for the selection process and CQP data. The sonographers graded the contrast uptake inside each plaque on a five-grade scale and the average result of the two sonographers was used for the correlation analysis. The correlation coefficient between CQP values and visual assessment was used to select the best noise reduction algorithm.

Correlation coefficients ranged from 0.59 to 0.93 depending on which time-intensity thresholds were used. The highest correlation was obtained when we defined pixels as white if their intensity was >35 at least 14% of the time. The selected algorithm was then validated by testing the ability of the program to identify the degree of contrast uptake by comparing the visual assessment with CQP values in a consecutive series of 48 plaques from 45 subjects. To achieve a consecutive series of examinations, seven of the plaques came from the CQP training data set. Validation data were analysed both with and without these seven plaques. Blinded evaluation of visual uptake served as a reference.

In some plaques, strong hyper-echogenic areas appeared inside the plaque when imaged using CPS (see Fig. 1B and C). The areas showed a strong echo signal even when no contrast was given and flared up when contrast was present. We consider these areas to be artefacts, which the CPS cannot filter. We performed the CQP analysis both with and without these areas. We excluded these areas both manually and by using an automatic algorithm that we developed. The automatic algorithm calculates the mean intensity in the reference area in every frame (see above); for every frame, pixels inside the plaque that show intensity higher than the mean value are considered as artefacts.

CQP and plaque vulnerability

The CQP was used to analyze plaques in a consecutive series of 52 subjects, of which the first 45 subjects came from the validation group. In subjects with more than one identified plaque, the plaque with the largest surface area was chosen. Data on previous clinical events were collected from patient records and the detailed questionnaire.

Reproducibility

To assess reproducibility we examined the first 20 subjects from the total group of 52 subjects in which we were able to perform two successful contrast examinations of the same plaque in the same insonation angle separated by a 30-min washout period. The washout time was set at

30 min because there was no visually detectable contrast left in any of the subjects after this time.

Statistical methods

The SPSS 20 statistical software package was used. Continuous data are presented as median and interquartile range (IQR). Mann-Whitney U test was used for paired comparisons. Correlations were evaluated using Spearman correlation coefficients. Reproducibility was evaluated using limits of agreement and intra class correlation and Bland-Altman plots. ANOVA or Kruskall-Wallis H test were used where appropriate. Power calculations were made using t-test. $P < 0.05$ (two-sided) was considered to be statistically significant.

RESULTS

Recruitment

Between January 2010 and June 2011, a total of 787 patients gave informed consent to enter the WINGA database. Of these, 514 (65%) had one or more carotid plaques, 237 (30%) had a plaque with a height of at least 2.5 mm and 162 (21%) had a plaque suitable for contrast examination (<10% acoustic shadowing). Of these 162 patients, 72 patients (9% of the total) met the inclusion and exclusion criteria and 40 patients gave informed consent to CEUS examination. Thirty-three of these patients were examined with CEUS and 30 patients were included in the current study. These 30 participants had a slightly lower plaque echogenicity compared with the 42 patients who met the inclusion and exclusion criteria but were not examined by CEUS, but this difference was not significant, and there were no differences in plaque size, age or gender (data not shown).

In the non-hospital-based recruitment of healthy volunteers, a total of 310 healthy volunteers were screened and 22 (7%) fulfilled the criteria for inclusion and participated in the study. In total, 52 subjects were included in the analysis contributing a total of 55 plaques. Characteristics of the subjects are shown in Table 1.

Adverse events

One subject experienced a short period of itching in the hands lasting up to one minute after contrast administration.

Validation of CQP

The validation data set consisted of 48 plaques. Five of these plaques were deemed "not suitable for visual assessment of contrast uptake" by one or both sonographers, and were excluded from the analysis. The final validation set thus comprised 43 plaques from 41 subjects. Characteristics of the validation group are shown in Table 1. Reproducibility analyses showed moderate inter-observer agreement between the two visual observers, weighted kappa = 0.58. The average result of the two visual observers was then used for analyzes.

The visual assessment of CEUS uptake correlated with non-corrected CQP values ($r = 0.64$, $r < 0.001$) and with CQP values corrected for visually detected artefacts ($r = 0.68$, $p < 0.001$; Fig. 2) and automatically detected artefacts ($r = 0.65$, $p < 0.001$). When the seven plaques that were part of the training set were excluded, the

Table 1. Characteristics of subjects according to experimental group. Continuous variables are presented as median and inter quartile range.

	All subjects $n = 52$	Validation group $n = 41$	Reproducibility group $n = 20$	[a]*p*-value
Age (years)	68 (63–72)	68 (63–72)	67 (62–72)	0.43
Sex (Female)	35%	33%	55%	0.20
Weight (kg)	79 (65–90)	78 (65–90)	72 (60–85)	0.34
BMI (kg/m^2)	24.8 (22.8–27.6)	25.1 (22.9–27.6)	23.8 (21.5–26.9)	0.48
Systolic blood pressure (mmHg)	138 (128–146)	138 (130–148)	137 (127–147)	0.59
Diastolic blood pressure (mmHg)	78 (68–80)	78 (69–81)	71 (60–80)	0.46
hs-CRP	1.41 (1.01–2.89)	1.42 (0.96–3.01)	1.34 (0.9–2.32)	0.93
Serum cholesterol (mmol/L)	5.2 (4.4–6.2)	5.2 (4.3–6.3)	5.1 (4.7–6.2)	0.91
Serum LDL cholesterol (mmol/L)	3.0 (2.1–4.0)	2.8 (2.1–4.0)	2.9 (2.1–4.0)	0.95
Serum HDL cholesterol (mmol/L)	1.74 (1.4–2.2)	1.7 (1.4–2.2)	1.8 (1.4–2.3)	0.81
Current smoking	23%	19%	20%	0.93
Previous smokers	27%	28%	20%	0.93
Never smokers	50%	54%	60%	0.93
History of Diabetes	8%	2%	5%	0.50
History of Hypertension	64%	70%	75%	0.61
History of Myocardial Infarction	8%	7%	5%	0.92
History of Stroke or TIA	50%	51%	50%	0.99
History of Ipsilateral Stroke or TIA	19%	16%	20%	0.91
Statin treatment >3months	35%	37%	35%	0.97
Anti platelet treatment >3 months	38%	37%	35%	0.97
Warfarin treatment >3 months	6.5%	9.3%	5%	0.80

[a] ANOVA or Kruskall-Wallis H test or Pearson Chi-square when appropriate.

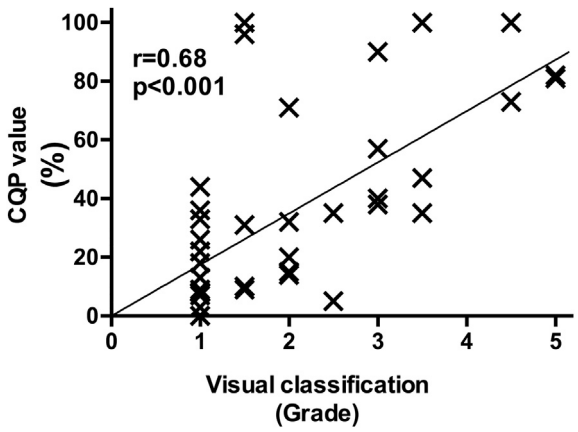

Figure 2. Correlation between CQP values (invalid areas manually excluded) and visual classification in the validation data set ($n = 43$ plaques from 41 subjects).

corresponding correlation coefficients were $r = 0.51$, $r = 0.60$ and $r = 0.55$ (all $p < 0.001$). We also observed that CQP values were skewed towards low values suggesting low contrast uptake in most of the plaques (Fig. 3).

Artefacts were found in almost every plaque using the automatic algorithm; however, most of them were very small. Visually detected artefacts were found in 43% of the plaques. These plaques were significantly smaller than those without artefacts (median area 28 mm^2 IQR 23—44 vs 40 mm^2 IQR 25—60, $p = 0.02$). No significant difference in plaque location was seen: 33% of plaques with artefacts were found in the near wall compared with 39% of plaques without artefacts. We did not observe any difference in echogenicity between plaques with and without artefacts when we used GSM (41 IQR 28—63 vs 36 IQR 28—52, $p = 0.37$); however, plaques with artefacts had a slightly higher echogenicity when assessed using PW (29 IQR 15—38 vs 17 IQR 9—28, $p = 0.04$).

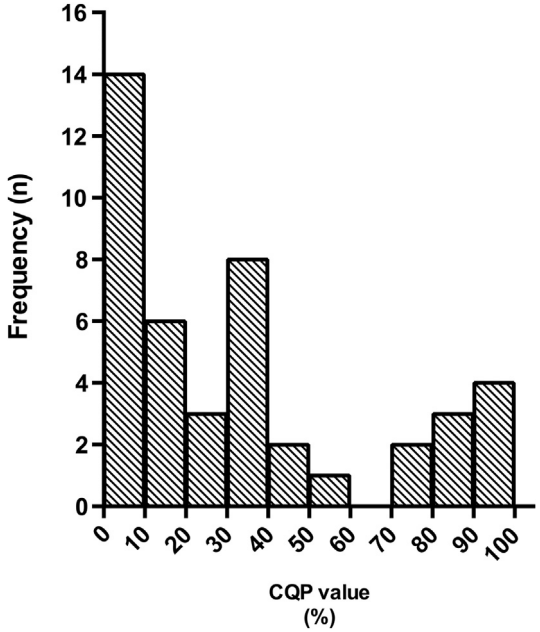

Figure 3. Distribution of CQP values in the validation data set ($n = 43$ plaques from 41 subjects).

Reproducibility of CQP

Characteristics of the 20 subjects included in the reproducibility study are shown in Table 1. Repeated analysis of a single examination showed a high intra-observer reproducibility with no systematic difference between the first and second CQP analyses (Fig. 4A). Analysis of the first and second examinations separated by a 30-min washout showed a high inter-observer reproducibility with no systematic difference between the two examinations (Fig. 4B). Based on the standard deviation measured in the inter observer-variability study we made a power calculation for a hypothetical treatment study with CQP value as primary outcome. We assumed a 10% decline of CQP value in the treatment group and no change in the placebo group. These assumptions give 80% power to detect 10% changes in contrast uptake if 30 patients are included in each group.

Contrast uptake is associated with echogenicity and history of clinical symptoms

After developing and validating the CQP, we used this technique to analyse plaques in our total population of 52 consecutively recruited subjects and compared CQP values

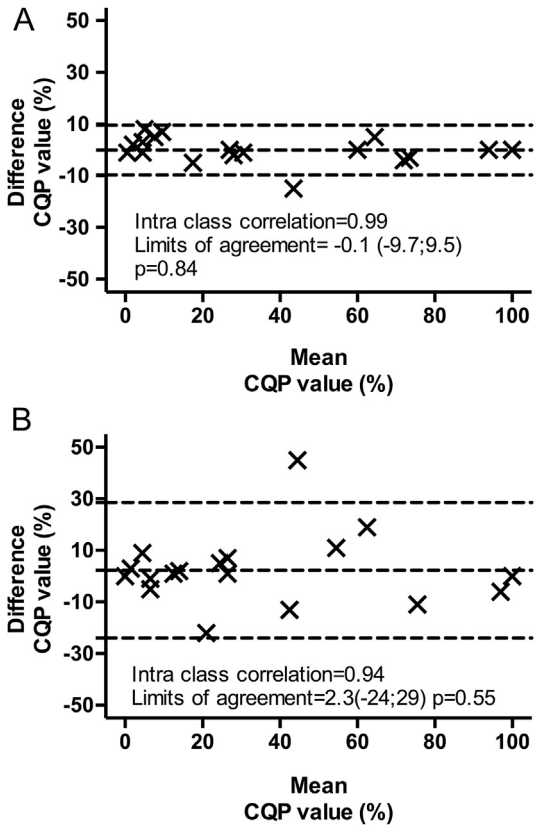

Figure 4. A: Bland-Altman plot showing differences between repeated analyses of a single examination. B: Bland-Altman plot showing differences between first and second examinations performed with 30-min wash-out period between examinations ($n = 20$).

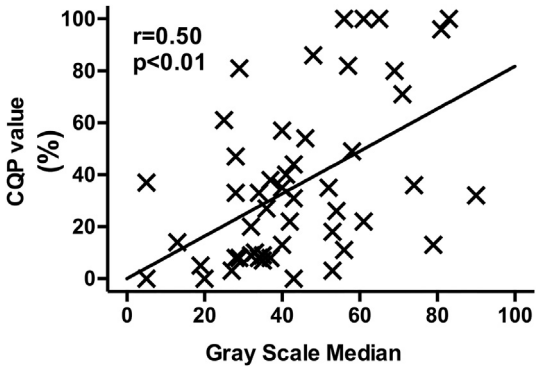

Figure 5. Correlation between Grey Scale Median and CQP values in all subjects ($n = 52$).

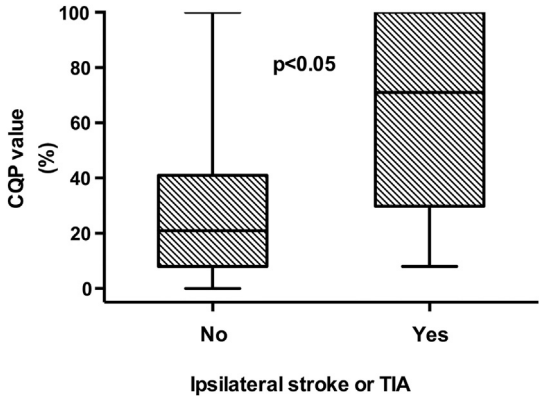

Figure 6. Box plot showing CQP values for subjects without history of ipsilateral stroke or TIA ($n = 42$) and with history of ipsilateral stroke or TIA ($n = 10$). Box perimeters indicate 25th and 75th percentile. Horizontal line inside box indicates median. Antennas outside box indicate range.

with echogenicity (measured using B-mode ultrasound imaging) and previous clinical events (shown in Table 1).

Most of the plaques in our study had low echogenicity with 61% of plaques assigned a Gray-Weale score of 1 or 2. Surprisingly, we observed significant positive correlations between CQP values and plaque echogenicity classified by GSM (Fig. 5) and by Gray-Weale and PW (data not shown) Table 2.

We observed a tendency toward higher CQP values in subjects with previous history of symptoms regardless of type of event compared with asymptomatic individuals (data not shown). This tendency reached statistical significance in subjects with a history of ipsilateral stroke/TIA (Fig. 6). In contrast, there were no differences between groups in plaque characteristics derived from B-mode imaging.

It has been shown that contrast uptake in far-wall plaques may be artifactually enhanced by so-called pseudo-enhancement.[22] To address this we analysed far- ($n = 31$) and near-wall ($n = 21$) plaques separately. We observed significantly higher CQP values in far-wall plaques than near-wall plaques (35 IQR 20–71 vs. 10 IQR 5–37,5, $p = 0.007$). However, when near and far-wall plaques were analyzed separately there was still a significantly higher CQP in the symptomatic plaques in the far-wall ($p = 0.048$) and a strong tendency for a higher CQP in symptomatic plaques in the near wall ($p = 0.08$) compared to asymptomatic plaques.

DISCUSSION

Here we describe a standardised examination protocol to objectively measure ultrasound contrast uptake in carotid plaques. The values obtained using our semi-automated method correlated with visual assessment of contrast uptake and were reproducible. Furthermore, we showed that contrast enhancement measured with our semi-automated method correlated with plaque echogenicity (measured using standard ultrasound imaging) and with previous cerebrovascular symptoms.

Earlier reports that measure contrast uptake used a semi-quantitative visual approach.[12,13,15,16,18] Although the semi-quantitative data correlate well with histological estimates of vascularisation,[12,14,15] the interpretation is highly user dependent and not suitable for multi-centre trials or serial

Table 2. Characteristics of plaques according to experimental group.

	All subjects $n = 52$	Validation group $n = 43$	Reproducibility group, $n = 20$	[a]p-value
Plaque area (mm^2)	33.8 (25.2–44.3)	33.5 (24.4–42.7)	33.1 (23.2–42.1)	0.89
Plaque height (mm)	3.47 (2.98–4.04)	3.42 (2.96–3.77)	3.37 (2.98–3.72)	0.81
Plaque location (near wall)	40%	42%	35%	0.87
Percentage White (%)	21 (12–33)	20 (12–32)	29 (17–40)	0.43
Grey Scale Median	40 (29–56)	40 (29–55)	43 (33–41)	0.41
Gray-Weale class I (echolucent)	28%	26% (11)	21%	0.99
Gray-Weale class II (Mostly echolucent)	67%	65% (28)	68%	0.99
CQP (%) Manually invalid area exclusion	29 (9–53)	22 (8–47)	27 (9–79)	0.86
CQP (%) Automatic invalid area exclusion	30 (8–53)	29 (7–51)	30 (9–76)	0.81
CQP (%) Without invalid area exclusion	32.5 (9–59)	32 (9–63)	37 (101–79)	0.74

[a] ANOVA or Kruskall-Wallis H test when appropriate.

examinations. Here, we established an objective software platform that addresses a number of specific requirements. In our experience, the appearance of contrast agent in the plaque over time is heterogeneous and, in most cases, an erratic process that cannot be modelled with standard inflow equations. Furthermore, the technique needs to overcome the movement artefacts generated by breathing, the cardiac cycle and small movements of the transducer. We found that insonation using a fixed image plane crossing the centre of the vessel at maximum plaque height generated long stable image loops suitable for interpretation after manual correction of movement artefacts. We analysed 90-s loops and showed that by choosing a suitable time-intensity threshold, the small changes in contrast uptake introduced by small movements of the transducer and plaque were averaged out. Using this technique, we generated reproducible data in good agreement with visual semi-quantification. Our reproducibility data show that the technique has an 80% power to detect 10% changes in contrast uptake if 30 patients are included in each group. Furthermore, it has been suggested that pseudoenhancement of contrast uptake affects plaques in the far wall of the carotid artery.[22] This phenomenon can also be found in our data but does not seem to affect interpretation of relative changes in CQP values.

How applicable is this technique to patients with atherosclerotic carotid disease? Its use is limited to patients with carotid plaques of a certain size and without much acoustic shadowing. In the current study, we found that 9% of the hospital-based population and 7% of the healthy population had plaques that were suitable for contrast examination. Thus, if the technique proves valuable to identify high-risk patients, it could be used in large patient groups as a tool for risk stratification.

It's possible that CEUS could be used to determine vulnerability within the group of plaques with low GSM. CEUS is only suitable for plaques with little acoustic shadowing and therefore the average GSM in our plaques is rather low. Previous prospective studies suggest that low echogenicity is associated with a more vulnerable plaque phenotype.[5,6] In our group of low echogenicity plaques we found a weak but significant positive correlation between contrast uptake in the plaque and echogenicity. This could be a random finding, but it can also suggest that low contrast uptake (and thus low vascularisation) may indicate a higher risk of future events. This interpretation is contradictory to previous reports showing that high contrast uptake is found in patients with a more vulnerable plaque phenotype.[13,16,18] It is also contradictory to our finding that contrast uptake was significantly higher in patients with a previous ipsilateral embolic stroke. Future prospective studies using CEUS are required to test if CEUS is a predictor of vulnerability.

In our population the CQP values were skewed towards lower levels: 44% of the plaques had CQP values below 20%. This may be explained by the accumulation of plaques with low echogenicity in our study population. Plaque with low echogenicity most likely have a large lipid-rich necrotic core,[23] which is not vascularized,[1] thus limiting the possibility for contrast uptake.

Limitations

Correlation of CQP with visual assessment deteriorated when the 7 training cases are deleted. This is probably due to the limited size of the training set. Because of the small number of plaques, it was not possible to perform multivariable analysis and to analyse sub-groups. Our primary aim with this paper was to develop a standardised technique for CEUS studies. The study was not specifically designed to test if vascularisation associates with other indices of risk. Although our observation that contrast uptake was significantly higher in patients with a previous ipsilateral embolic stroke is in agreement with previous reports,[13,16,18] the current analyses and previous reports were done on cross-sectional data and we do not have information on the predictive value of increased contrast uptake. As we have previously shown, vascularisation increases with time after the event and may thus be associated with healing,[24] which complicates interpretation of data. These data should also be interpreted with caution given the low number of observations and the mixed subject group.

CEUS as a tool has several limitations that needs to be taken into account: *i.* imaging is done using a hand held transducer which introduces user dependency, *ii.* contrast uptake can not be monitored in areas of the plaque shadowed by calcifications, *iii/*the phenomenon of pseudoenhancement may affect imaging of plaques in the far and near wall differently.

Conclusion

We have presented an eligible method to measure contrast uptake in human carotid plaques, which can be applied to large populations. The method offers a reproducible and objective way to identify contrast uptake in carotid plaques and to use as an index of vascularisation. Furthermore, contrast uptake is higher in subjects with a history of recent ipsilateral embolic stroke. A critical evaluation of the clinical value of contrast uptake to identify vulnerable plaques in patients at risk of future cerebrovascular events is important.

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CONFLICT OF INTEREST

None.

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