Validation of Noninvasive In Vivo Compound Ultrasound Strain Imaging Using Histologic Plaque Vulnerability Features

Hendrik H.G. Hansen, PhD; Gert Jan de Borst, MD, PhD; Michiel L. Bots, MD, PhD; Frans L. Moll, MD, PhD; Gerard Pasterkamp, MD, PhD; Chris L. de Korte, PhD

Background and Purpose—Carotid plaque rupture is a major cause of stroke. Key issue for risk stratification is early identification of rupture-prone plaques. A noninvasive technique, compound ultrasound strain imaging, was developed providing high-resolution radial deformation/strain images of atherosclerotic plaques. This study aims at in vivo validation of compound ultrasound strain imaging in patients by relating the measured strains to typical features of vulnerable plaques derived from histology after carotid endarterectomy.

Materials and Methods—Strains were measured in 34 severely stenotic (>70%) carotid arteries at the culprit lesion site within 48 hours before carotid endarterectomy. In all cases, the lumen-wall boundary was identifiable on B-mode ultrasound, and the imaged cross-section did not move out of the imaging plane from systole to diastole. After endarterectomy, the plaques were processed using a validated histology analysis technique.

Results—Locally elevated strain values were observed in regions containing predominantly components related to plaque vulnerability, whereas lower values were observed in fibrous, collagen-rich plaques. The median strain of the inner plaque layer (1 mm thickness) was significantly higher (P<0.01) for (fibro)atheromatous (n=20, strain=0.27%) than that for fibrous plaques (n=14, strain=-0.75%). Also, a significantly larger area percentage of the inner layer revealed strains above 0.5% for (fibro)atheromatous (45.30%) compared with fibrous plaques (31.59%). (Fibro)atheromatous plaques were detected with a sensitivity, specificity, positive predictive value, and negative predictive value of 75%, 86%, 88%, and 71%, respectively. Strain did not significantly correlate with fibrous cap thickness, smooth muscle cell, or macrophage concentration.

Conclusions—Compound ultrasound strain imaging allows differentiating (fibro)atheromatous from fibrous carotid artery plaques. (Stroke. 2016;47:2770-2775. DOI: 10.1161/STROKEAHA.116.014139.)

Key Words: atherosclerotic plaque ■ carotid artery diseases ■ elasticity imaging techniques ■ lipids ■ stroke ■ ultrasonography

Atherosclerotic carotid plaque rupture is a major cause of cerebrovascular mortality and morbidity. The proneness of a plaque to rupture is mainly related to its composition and geometry.1,2 Rupture-prone plaques typically contain a medium to large necrotic/lipid-rich core, which is separated from the lumen by a thin fibrous cap, whereas stable plaques have a thicker cap and often no necrotic/lipid-rich core.1,2 Furthermore, vulnerable plaques frequently present with intra-plaque hemorrhage, a high concentration of macrophages, and a decreased number of smooth muscle cells (SMCs).3,4 Local features of plaque vulnerability are correlated with an increased risk of future cerebrovascular events (CVE).4,5 This explains why local detection of these features is important. Detection of local features might also serve as a surrogate marker for plaque progression and subsequent CVE in other vascular beds. For instance, catheter-based techniques such as virtual histology or near-infrared spectroscopy have demonstrated that detection of lipid in the vascular tree has potential for accurate risk stratification of patients with acute coronary syndromes.6 However, because plaques are often asymptomatic before the first CVE, a patient-friendly noninvasive technique is required. Ultrasound is nonionizing, fast, and relatively inexpensive, and, therefore, has many advantages for assessment of plaque characteristics. Unfortunately, conventional ultrasound does not allow an accurate determination of the ratio of lipids and fibrous tissue throughout the plaque.

A relatively new technique is ultrasound strain imaging, also referred to as elastography or palpography,3,7–13
Vascular strain imaging estimates deformations/strains in the plaque and arterial wall induced by the pulsating blood. As intravascular studies have shown, strain values differ significantly for fibrous, fibroatheromatous, and atheromatous plaques. Furthermore, an increased number of high strain spots was found in coronary arteries of patients with unstable angina pectoris compared with patients with stable angina. Although one study reported that strain values did not differ between plaques in patients with and without major adverse cardiac events, in that study, strain parameters of all plaques of a patient were averaged that probably masked the increased strain regions present in the plaque responsible for the event. A noninvasive technique would have allowed checking which characteristics the plaque had that actually ruptured. With a noninvasive technique, also long-term monitoring to study the effectiveness of treatment on local plaques will become available. Lately, noninvasive variants were introduced for carotid arteries, mostly for longitudinal imaging planes. However, able. Lately, noninvasive variants were introduced for carotid arteries, mostly for longitudinal imaging planes.9–12

#### Carotid Endarterectomy and Histological Analysis

During carotid endarterectomy, the vascular surgeon made a longitudinal incision on the ventral side of the plaque, after which the intima and media layer containing the plaque were excised. The culprit lesion segment was identified using the aforementioned caliper distance and cut and stained with 5 different stainings according to the procedures of a Biobank study called Athero-express:10–20 CD68, α-actin, picrosirius red, hematoxylin and eosin, and Elastin van Gieson. On the basis of the stained slices, an expert (G.P.) blinded to the strain results scored 4 distinct plaque characteristics: plaque phenotype (fibrous or (fibro)atheromatous), SMC concentration, macrophage concentration, and cap thickness (thin or intermediate to thick). Percentage concentration of macrophages and SMCs were determined on a continuous scale using the previously published quantitative analysis.1,21 The other characteristics were analyzed semiquantitatively. A plaque’s phenotype was classified as fibrous when a plaque had no lipid core or a small (10% of plaque area) lipid core, low macrophage infiltration, and high SMC and collagen content; otherwise, it was classified as (fibro)atheromatous. Although fragments of thrombus, intraplaque bleeding, and calcifications were occasionally observed in the stained slices, these components were not used for analysis, because it was questionable if these components remained present throughout the endarterectomy and histological preparation.

The orientation and rotation of the slices with respect to the ultrasound recordings was determined before strain estimation using photographs taken during the plaque preparation process (before and after slicing) together with the echograms (calculated from the radiofrequency data). If present, the location of calcifications was also used to deduce the orientation of the slice with respect to the echograms. Ten arteries were excluded from analysis. Two because the plaque became fragmented during preparation, which impeded proper histological analysis. Two because the imaged cross-section obviously did not match with the histology slice. Five because the lumen–vesel boundaries could not be identified on the ultrasound images and 1 because the longitudinal motion of the artery caused the imaged cross-section to move out of plane from systole to diastole.

#### Radial Strain Estimation

Radial strain estimation was performed off-line using custom-made software (MATLAB 2010b, Mathworks, Natick, MA). First, ultrasonic frames were identified that corresponded to the systolic and diastolic phases (maximum and minimum lumen diameters derived from a diameter curve obtained by postprocessing, respectively). Next, from the 3 seconds acquisition, the pressure cycle (systole to systole), which visually showed the least out-of-plane motion, was selected.
for strain analysis for each patient. Within this cycle, the cumulative radial wall strain was determined from systole to diastole using a coarse-to-fine 2-dimensional cross-correlation–based displacement estimation algorithm followed by displacement compounding, tracking, rotation, and 2-dimensional least-squares strain estimation. For detailed settings of the algorithm, please see Table I in the online-only Data Supplement. All strain estimation was performed on raw ultrasound radiofrequency data, because the phase information of the radiofrequency data allows more accurate strain estimation than can be obtained when using envelope or B-mode data. A strain value was obtained for every 62.5 and 200 μm of tissue in the vertical and horizontal directions, respectively. Because the amount of deformation is not only related to tissue stiffness but also to the force applied to the tissue, all strains were normalized with respect to a reference pulse pressure $P_{\text{ref}}$ of 5333 Pa (40 mm Hg):

$$
\varepsilon_{\text{norm}} = \frac{P_{\text{sys}} - P_{\text{dia}}}{P_{\text{ref}}} \varepsilon_{\text{meas}}
$$

where $\varepsilon_{\text{meas}}$ and $\varepsilon_{\text{norm}}$ are the estimated and normalized strain, and $P_{\text{sys}}$ and $P_{\text{dia}}$ are the brachial systolic and diastolic pressures in Pascals (Pa) for a certain patient. As a final result, the algorithm provided a color-coded image (similar to Color Doppler) representing the radial strain from systole to diastole (Figures 1C, 2C, and 3C). Yellow and black indicate wall thickening and thinning (in radial direction), respectively, in these images.

**Analysis**

First, a qualitative comparison (visual match) between the strain images and the histological composition of plaques was performed to assess whether increased radial strains matched with histologically vulnerable plaque regions. Because the ultimate goal is to have one value based on the strain image that identifies whether a plaque is vulnerable or not, 2 types of parameters were defined: a percentile strain parameter: the xth-percentile of the strain values (25th, 50th, 75th, 90th, 95th, and 99th percentile), and a high strain area parameter: the percentage of strain values (representing an area) exceeding a certain strain level. On the basis of the obtained strain images, strain levels of 0.0%, 0.5%, 1.0%, and 1.5% were tested. Because strain for tissue distal from the lumen is not only related to the local plaque composition but also to the tissue composition in between this location and the lumen, only strain values within a 1-mm-thick ring adjacent to the lumen–plaque border were considered when calculating the parameter values. Plaque rupture that leads to thrombus formation and causes CVE is also expected to occur in this ring. The performance of both parameters to differentiate between the categories of the semiquantitative histological parameters was quantified by calculating the area under the curve (AUC) of receiver–operator characteristics curves. The percentile- and strain-level settings that resulted in the highest mean AUC were considered as the optimal settings for a certain parameter. At these settings, sensitivity, specificity, positive predictive value, and negative predictive value were calculated for the point with the highest Youden index. To determine whether the AUC significantly deviated from 0.5, binomial exact confidence intervals were calculated. Also, Mann–Whitney tests were performed to detect statistically significant differences ($P$<0.01) in strain parameter values for these semiquantitative parameters. For the quantitative histology parameters, the optimal percentile- and strain-level settings were determined by calculating Spearman correlation coefficients. All statistical analyses were performed using SPSS Statistics version 20 (IBM, Armonk, NY).

**Results**

**Histological Results**

Fourteen plaques were classified as fibrous and 20 as fibro(atheromatous). Thirteen had a thin cap and 18 a thick cap. In 3 cases, the cap thickness could not be estimated from the staining. SMC concentration could also not be determined for 1 plaque.

**Strain Results**

Typical examples of strain images and corresponding histology of different plaques are presented in Figures 1 through 3. In general, locally elevated strain values were observed in regions that predominantly contained vulnerability-related components according to histology, whereas lower values were observed in fibrous, collagen-rich regions. The AUC and cross-correlation results for all settings of both strain parameters for all histological features are presented in Tables II and III in the online-only Data Supplement. For the 50th percentile, the strain percentile parameter had the highest AUC for plaque phenotype differentiation. The AUC was 0.78 with a binomial exact confidence interval ranging from 0.61 to 0.94 and significantly deviated from 0.5 ($P$=0.0012). Receiver–operator characteristics analysis for this parameter for the detection of (fibro)atheromatous plaques resulted in a sensitivity of 85%, a specificity of 64%, a positive predictive value of 77%, and a negative predictive value of 75% at a threshold strain of −0.45%. For the high strain area parameter, also the highest AUC (AUC=0.80, strain >0.5%) was observed for plaque phenotype. Again, the AUC was significantly higher ($P$=0.0005) than 0.5. The corresponding values for sensitivity, specificity, positive predictive value,

![Figure 1](http://stroke.ahajournals.org/)
and negative predictive value were 75%, 86%, 88% and 71%, respectively, at a threshold area of 37.3%. The Mann–Whitney tests also reveal a significant difference between the values of both strain parameters when differentiating between (fibro)atheromatous and fibrous plaques. For cap thickness, no significant difference in strain parameter values was found. Also, no significant correlation with SMC or macrophage concentration was observed.

Discussion
In this study, noninvasive CUSI was validated in patients using histological data of plaque specimen obtained with endarterectomy. The principal findings of this study are that: (1) strain parameters obtained with CUSI allow differentiation between fibrous and (fibro)atheromatous plaques, (2) noninvasive CUSI of carotid arteries is feasible in patients, and (3) no significant correlation was found between strain parameters and cap thickness, SMC concentration, or macrophage concentration.

Relation Between Strain and Histology
Both strain parameters were significantly higher for (fibro)atheromatous plaques than for fibrous plaques, which was also observed with intravascular elastography.1 Opposed to that study, no negative correlation with cap thickness was observed. Probably, this is because the plaques were obtained by endarterectomy in this study. Especially for thin caps, it is difficult to perform the excision and longitudinal cut without loss of cap material. Therefore, classification of the absolute cap thickness might be inaccurate, which might also explain the large variance in the AUC for this parameter. Also, no significant difference was found in strain for various concentrations of SMCs and macrophages. This might be because of the fact that strain is not a direct result of the presence of one histological component, but a representation of the interaction between all components. This is perfectly illustrated by the plaque shown in Figure 1, which contains a high concentration of macrophages and is simultaneously predominantly composed of collagen and SMCs. Because of the collagen and SMCs, this plaque is stiff resulting in low strain values despite the macrophages. This might also explain why plaque phenotype correlates best with the strain parameters because it takes into account multiple features of plaque vulnerability. The fact that strain not directly reflects the presence of a single plaque component was also the reason why we did not choose to quantify the degree of local matching between strain and histology. Nevertheless, regions that mainly consist of soft tissue and a high concentration of macrophages that destabilize the plaque integrity can be expected to deform more than collagen-rich regions, as confirmed by the images shown in Figures 1 through 3.

Comparison With Other Imaging Techniques
(Fibro)atheromatous plaques were detected with a sensitivity and specificity of 75% and 86%, respectively. Imaging modalities, such as magnetic resonance imaging and positron emission tomography–computed tomography have shown similar and occasionally higher values, although a one-to-one comparison with CUSI still has to be performed. For a discussion on the performance of these imaging modalities for vulnerable plaque imaging, we would like to refer to a recent review article.25 The main advantages of an ultrasound-based technique,
such as CUSI, are the short measurement times, the fact that is nonionizing, easily applicable, relatively inexpensive, and noninvasive. Therefore, CUSI might make screening for vulnerable plaques in patients in an earlier (subclinical) stage of atherosclerosis possible. CUSI might also be the first patient-friendly technique to study the effect of lipid-lowering medication at plaque level. Prospective studies such as the ECST-2 trial (http://www.ecst2.com), in which large populations with less advanced plaques are imaged and strain parameters are related to traditional cardiovascular risk factors and clinical parameters like an acute event or the need for an interventional procedure, are crucial to show the usefulness for cardiovascular risk stratification of the measured strain parameters. It would also be interesting to investigate whether the proposed strain parameters can be used as a surrogate marker for CVE when studying the effect of medication and interventions, as has also been done for intima–media thickness measurements.26

Limitations
Although extreme care was taken not to damage the tissue, 2 plaques were no longer intact after endarterectomy and histological preparation. In the surgical procedure, the arterial wall is longitudinally dissected, and during histological preparation, calcified plaques first undergo a decalcification step to enable microdissection. Both procedures affect plaque integrity and probably also affect the most vulnerable regions of the plaque. Consequently, histology-based vulnerability might have been underestimated for some vulnerable plaques and overestimated for calcified plaques, leading to mismatches with the strain-based classification and possibly to underestimation of the performance of the technique. During the endarterectomy, the specimens become deflated and cut, which influences geometry. This probably led to small mismatches in the alignment of the imaged and histology-stained cross-sections and, thus, also introduced noise in the performance analysis. En-bloc excision instead of the current excision procedure would have allowed a better preservation of plaque morphology, although it can only be performed safely in certain patients.

The optimal settings of the 2 strain parameters were chosen as those providing the highest area under the receiver–operator characteristics curves or Spearman correlation values. This procedure depends to a certain extent on the characteristics of the studied samples. Especially because the sample size was relatively small, this might have introduced some error in the performance assessment.

The final limitation that might have affected the performance assessment of the strain parameters is the fact that some histology parameters (phenotype and cap thickness) were determined semiquantitatively. Unfortunately, for these parameters, no quantitative methods were available yet. This might have made the analysis more objective and would have enabled calculation of correlation on a continuous scale. Nevertheless, as previous Athero-express studies have shown, the intra- and interobserver reproducibility of the semiquantitative analysis is moderate to substantial.20,21

Of the 10 excluded plaques, 6 were excluded because of technique-related issues. We only included cases (34 out of 40) for which the imaged cross-section remained in the imaging view from systole to diastole and for which the lumen–plaque boundary was identifiable on the B-mode data, because otherwise strain results would be based on noise. If we consider the studied cases to be representative of a standard population, this implies that the current implementation of the technique should not be used in 15% of cases. Future versions of CUSI might be developed to allow successful plaque differentiation in more cases. For instance, to deal with out-of-plane motion in future, the technique is being extended into the third dimension. For those cases in which plaques are located too deeply to have a proper delineation between lumen and plaque border (n=2 in this study), improvements in sensitivity of ultrasound equipment might be a solution. Acoustic shadowing caused by calcifications, which also lead to an unidentifiable lumen–plaque boundary in 3 cases, cannot be overcome by technical innovation. However, it should be noted that dense calcifications are mainly present in advanced plaques. Imaging at an earlier stage of atherosclerosis might not have this problem. As long as plaques are not smaller than 2 by 2 mm², which is the largest window size used by the algorithm, we expect the technique to have at least equal performance. Current clinical guidelines do not indicate a need for intervention when stenosis is <50%. At ≥50% stenosis, this size requirement is usually fulfilled.

As mentioned earlier, the entire protocol took 15 minutes followed by an off-line strain calculation. The off-line analysis requires user interaction and takes ≈2 hours per patient, which is too slow for routine clinical use. However, most commercial vendors have already incorporated real-time radiofrequency-based strain estimation using cross-correlations in their systems. Therefore, real-time CUSI should be feasible.

Summary
Noninvasive compound ultrasound strain imaging allows in vivo estimation of cumulative radial strains in transverse cross-sections of severely stenotic human carotid artery plaques. Local matches were observed between the strain patterns and the histology-based plaque composition. Furthermore, 2 strain parameters were defined that positively correlated with the presence of an atheromatous core. No significant correlation was found with fibrous cap thickness, SMC concentration, or macrophage concentration. Nevertheless, because the technique is noninvasive, easily applicable, relatively inexpensive, fast, and nonionizing, it seems promising for early assessment of carotid artery plaque vulnerability, although more studies are needed to fully explore its potential.

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Disclosures
None.

References
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Supplemental Tables

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<th>Setting</th>
<th>Iteration 1</th>
<th>Iteration 2</th>
<th>Iteration 3</th>
<th>Iteration 4</th>
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<td>Radial displacements</td>
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<td>9° x 0.5 mm§</td>
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*Axial x lateral direction; †with sub-sample aligning; ‡filter settings after compounding for the cumulated horizontal and vertical displacements, respectively; §filter sizes defined in circumferential x radial direction, because of conversion to polar grid with a spacing of 1° circumferentially and 100 µm radially.
Table II. Performance of the strain parameters at different settings for detecting differences in histology-based plaque phenotype and cap thickness

<table>
<thead>
<tr>
<th>Strain parameter</th>
<th>Plaque phenotype (fibrous / (fibro)atheromatous)</th>
<th>Cap thickness (thick / thin)</th>
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<tr>
<td></td>
<td>AUC (CI)</td>
<td>Median (IQ values)</td>
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<tr>
<td>25th percentile</td>
<td>0.71 (0.53, 0.89)</td>
<td>-2.07 (-3.10, -1.38) / -1.27 (-2.30, -0.40)*</td>
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<tr>
<td>50th percentile</td>
<td><strong>0.78 (0.61, 0.94)</strong></td>
<td><strong>-0.75 (-1.04, -0.08) / 0.27 (-0.40, 1.36)</strong>*</td>
</tr>
<tr>
<td>75th percentile</td>
<td>0.74 (0.55, 0.93)</td>
<td>0.96 (0.09, 2.02) / 2.10 (1.28, 2.94)*</td>
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<tr>
<td>90th percentile</td>
<td>0.66 (0.47, 0.86)</td>
<td>2.48 (1.19, 4.49) / 4.07 (2.93, 5.45)</td>
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<td>95th percentile</td>
<td>0.63 (0.43, 0.83)</td>
<td>3.73 (2.16, 5.89) / 5.42 (4.04, 7.39)</td>
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<td>99th percentile</td>
<td>0.58 (0.38, 0.79)</td>
<td>5.30 (3.35, 9.31) / 6.96 (5.54, 10.24)</td>
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<td>Area strain&gt; 0.0%</td>
<td>0.78 (0.61, 0.94)</td>
<td>38.81 (27.67, 48.32) / 55.02 (43.72, 70.83)*</td>
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<td>Area strain&gt; 0.5%</td>
<td><strong>0.80 (0.63, 0.96)</strong></td>
<td><strong>31.59 (16.07, 37.09) / 45.30 (36.03, 63.64)</strong>*</td>
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<td>Area strain&gt; 1.0%</td>
<td>0.76 (0.59, 0.94)</td>
<td>24.49 (11.57, 32.08) / 39.44 (29.02, 55.77)*</td>
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<td>Area strain&gt; 1.5%</td>
<td>0.73 (0.55, 0.90)</td>
<td>17.83 (8.43, 27.50) / 32.59 (21.18, 46.73)*</td>
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*P < 0.01 (Mann-Whitney test). AUC = area under the receiver-operating-characteristics curve, CI = binominal exact confidence interval, and IQ = interquartile.
Table III. Performance of the strain parameters at different settings for detecting differences in the histology-based concentration of macrophages and smooth muscle cells

<table>
<thead>
<tr>
<th>Strain parameter</th>
<th>Macrophage concentration (low / high)</th>
<th>Smooth muscle cell concentration (high / low)</th>
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<td>90th percentile</td>
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<tr>
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<tr>
<td>99th percentile</td>
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Supplemental References

