DOI: 10.1111/echo.12348
Echocardiography

Asymptomatic Carotid Disease—A New Tool for Assessing Neurological Risk

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Active carotid plaques are associated with atheroembolism and neurological events; its identification is crucial for stroke prevention. High-definition ultrasound (HDU) can be used to recognize plaque structure in carotid bifurcation stenosis associated with plaque vulnerability and occurrence of brain ischemic events. A new computer-assisted HDU method to study the echomorphology of the carotid plaque and to determine a risk score for developing appropriate symptoms is proposed in this study. Plaque echomorphology characteristics such as presence of ulceration at the plaque surface, juxta-luminal location of echolucent areas, echoheterogeneity were obtained from B-mode ultrasound scans using several image processing algorithms and were combined with measurement of severity of stenosis to obtain a clinical score—enhanced activity index (EAI)—which was correlated with the presence or absence of ipsilateral appropriate ischemic symptoms. An optimal cutoff value of EAI was determined to obtain the best separation between symptomatic (active) from asymptomatic (inactive) plaques and its diagnostic yield was compared to other 2 reference methods by means of receiver-operating characteristic (ROC) analysis. Classification performance was evaluated by leave-one-patient-out cross-validation applied to a cohort of 146 carotid plaques from 99 patients. The proposed method was benchmarked against (a) degree of stenosis criteria and (b) earlier proposed activity index (AI) and demonstrated that EAI yielded the highest accuracy up to an accuracy of 77% to predict asymptomatic plaques that developed symptoms in a prospective cross-sectional study. Enhanced activity index is a noninvasive, easy to obtain parameter, which provided accurate estimation of neurological risk of carotid plaques. (Echocardiography 2014;31:353–361)

Key words: stroke, carotid plaque, asymptomatic carotid disease, enhanced activity index, ultrasound, speckle, risk

Carotid bifurcation disease is responsible for one third of acute cerebrovascular events caused by atheroembolization in the internal carotid artery territory.[1,2] Symptomatic disease with transient ischemic attacks carries a high risk of stroke which is higher in the first 2 weeks following the first clinical episode. Asymptomatic carotid stenosis is usually benign presenting a stroke risk of 3% per year. However, a significant number of high life expectancy patients may suffer a stroke often without warning symptoms.[3] Severity of stenosis (>70%) was shown to be associated with higher risk of ipsilateral stroke in both symptomatic and asymptomatic patients, regardless of lipid lowering treatment with statins.[3] However, using only severity of stenosis as a single criterion to select patients for intervention in asymptomatic carotid disease requires a high number of unnecessary carotid interventions to prevent a single stroke.[4] Several published reports have associated plaque morphological features to plaque vulnerability and rupture, leading to thrombosis and cerebral embolism, and to a higher risk of ipsilateral neurological events and stroke[5,6] and recently it was suggested that stratification of stroke risk in

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patients with asymptomatic carotid disease based upon clinical parameters and plaque structure features was feasible.[3]

Identification of active carotid lesions, prone to develop thrombotic events and associated with increased stroke risk became a major objective to identify patients that would benefit from a carotid intervention to prevent stroke.

Pathological studies have shown that intra-plaque hemorrhage, juxta-luminal location of lipid necrotic core, and the presence of ruptured endothelial surface are markers of clinically active plaque[8,9] and presence of appropriate symptoms.

Imaging of carotid bifurcation lesions to assess its morphology and biological activity is a very active and promising area for research and clinical use. Morphological imaging using ultrasound, CT, or MRI have been described to study plaque texture, presence of subendothelial hemorrhage, cholesterol deposits, and the presence of calcification.[10] Biological imaging using isotope techniques have aimed to target markers of active inflammation process, which is associated with plaque instability.[11] However, CT and MR scans are expensive and time-consuming technologies not easy to perform in a busy clinical setting, and biological imaging based upon uptake of radioactive components (FDG) involves radiation, is invasive, expensive, and it has been used essentially for experimental research, without routine clinical application.

Ultrasound imaging with Doppler flow evaluation is an effective imaging modality for early assessing carotid stenosis and plaque structure[7] with the advantage of being noninvasive, nonionizing, inexpensive, and available at most medical facilities. The development of objective and quantitative tools to assess plaque echomorphology[6,8] helps in understanding the structural changes associated with biologically active lesions, leading to thromboembolic events and stroke.

Initial studies found that qualitative assessment of plaque echogenicity and texture obtained from high-definition ultrasound (HDU) were positively correlated with neurological risk,[13–15] but its clinical application was limited because of lack of reproducibility and high observer/equipment dependency in data acquisition. Computer-assisted plaque analysis employing image normalization, ultrasound feature extraction, and powerful classification strategies provides a more objective assessment of the carotid disease.[6,9,12,16–19]

The authors introduced the activity index (AI) that combines quantitative and qualitative ultrasound features obtained from HDU and computer-assisted analysis. The AI showed a good correlation with appropriate ocular and neurological symptoms,[17] in particular the average score for symptomatic plaques was found to be 75 against 43 for asymptomatic plaques. Moreover, 78% of symptomatic plaques showed AI $>$ 60% and 70% of asymptomatic plaques had AI $<$ 50. Statistical tests performed with the Mann–Whitney *U*-test[27] reject the null hypothesis at 5% significance level that the 2 groups of plaques have identical AI distributions (equal medians) with a P-value = 9.5E-9.

In recent years, the importance of ultrasound speckle for tissue characterization has been recognized,[20] particularly as a textural descriptor.[20–24] In this scope, the authors proposed a despeckling method[25,26] that decomposes the ultrasound B-mode image into noiseless and speckle components to extract echomorphology and textural descriptors, respectively, providing a more complete characterization of the carotid plaque.

This study proposes a new score, designated as enhanced activity index (EAI), which combines clinical parameters with ultrasound features obtained after a series of image-processing operations. This new score improves the early proposed AI[13] as it provides a more objective and complete characterization and risk stratification of carotid active plaques. The usefulness of the proposed score is investigated by means of a typical classification problem carried out on a population of symptomatic and asymptomatic plaques.

Material and Methods:

This study is based on ultrasound data obtained from patients observed through a medical consultation at the Cardiovascular Institute of Lisbon and at the Department of Vascular Surgery, Lisbon's Academic Medical Center. Evaluation with color-flow Duplex-scan of both carotids was performed with ATL-HDI 3000 or 5000 scanner (Philips Medical Systems, Bothell, WA, USA). Equipment setup included 5 to 12 MHz broadband linear-array transducer, 60 dB dynamic range, and postprocessing linear maps. Image acquisition included the most representative longitudinal cut in color and B-mode as selected by the operator (L.M.P.) who performed the HDU acquisitions. In addition, the presence of surface disruption, and/or of an echogenic cap overlying the lesion, the location of the echolucent region in heterogeneous lesions (central or juxta-luminal), and the degree of stenosis were determined and recorded. The degree of stenosis was quantified by morphological (cross-sectional area) and velocity criteria.[19]

Clinical examination assessed the neurological status and a plaque was considered symptomatic when amaurosis fugax (AF) or focal (transitory, reversible, or established) cerebral events in the ipsilateral carotid territory occurred

in the previous 6 months. The symptomatic/asymptomatic information is useful to compute and validate the proposed EAI.

Plaque Classification:
The workflow for computing and testing the EAI is based on a classification paradigm depicted in Figure 1. During the training phase, B-mode images are collected and normalized followed by region of interest (ROI) selection, image processing, and feature extraction from the defined ROIs, as presented in Figure 2. Significant features are identified using suitable statistical tests. Such features and the experts' ground truth about the plaque condition (symptomatic/asymptomatic) provide the training parameters that are used to obtain the EAI. Details on the computation of EAI are given in Appendix A.

The workflow for plaque classification based on the EAI is implemented through a computer-aided diagnosis system (CADx) designed in MATLAB (version 7.10.0; The MathWorks Inc, Natick, MA, USA). The CADx enables to: (i) visualize the acquired ultrasound data in real time, (ii) delineate the plaque(s) contour(s), and (iii) introduce clinical information concerning the studied plaque. Image processing/feature extraction module is performed automatically and the EAI is displayed. The workflow consisting of image processing, feature extraction, and calculation of the EAI takes approximately 30 sec per plaque on a dual core PC with 1.87 GHz processor. The time for plaque segmentation and input of clinical parameters by the medical doctor takes about 90 sec. A commercial version of the CADx by AtheroPoint LLC (Roseville, CA, USA) is being produced where the EAI is computed in real time.

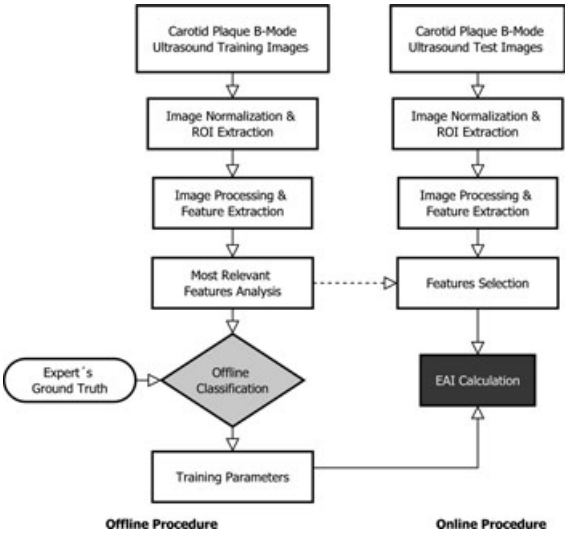

Figure 1. Block diagram of the workflow for determination of the enhanced activity index. The workflow consists of an offline training phase that considers all the data except that belonging to the patient whose score is to be computed.

Results:
The results are based on 146 carotid bifurcation plaques. The characteristics of the population are listed in Table I. We present 4 different results: first, we describe the set of ultrasound parameters required to characterize the plaque symptomatic condition and to compute the EAI; secondly, we investigate the distribution of the computed-enhanced activity indexes for each class of symptomatic and asymptomatic plaques. The third result compares the receiver-operating characteristic (ROC) curves obtained with the classification methods based on the proposed EAI together with the degree of stenosis and the AI. Finally, we benchmark the classification performance of each method based on the computed cutoffs.

EAI Significant Parameters:
The set of most significant features (P-value <0.05) identifying the active lesion is listed in Table II. This result highlights the importance of combining well-established morphological features with different sources of information extracted from processed ultrasound data to define and characterize the active carotid plaque. In particular, some of these features are extracted from the histogram of the normalized image, the statistical mixture model estimated on the envelope radiofrequency, and also the speckle component.

Plaque Distribution According to the EAI:
Investigation of the distribution of the carotid plaque scores brings up evidence of the usefulness of the proposed risk index since, as the result in Figure 3 shows, the asymptomatic plaques are predominantly located in the index interval 20–30 while most of the symptomatic plaques show a risk higher than index 55 (P-value <0.01). This score can be used by clinicians as a first indication of plaque severity. This is an important outcome of the method because it provides a quantitative measure to help the clinician in making a diagnosis rather than simply outputting a symptomatic versus asymptomatic classification.

ROC Curves for Degree of Stenosis, AI, and EAI:
ROC curve analysis is useful to compare the performance of the studied diagnostic markers (degree of stenosis, AI, and EAI) and further, to select a cutoff value for diagnostic decision making. Details on ROC curve analysis are given in

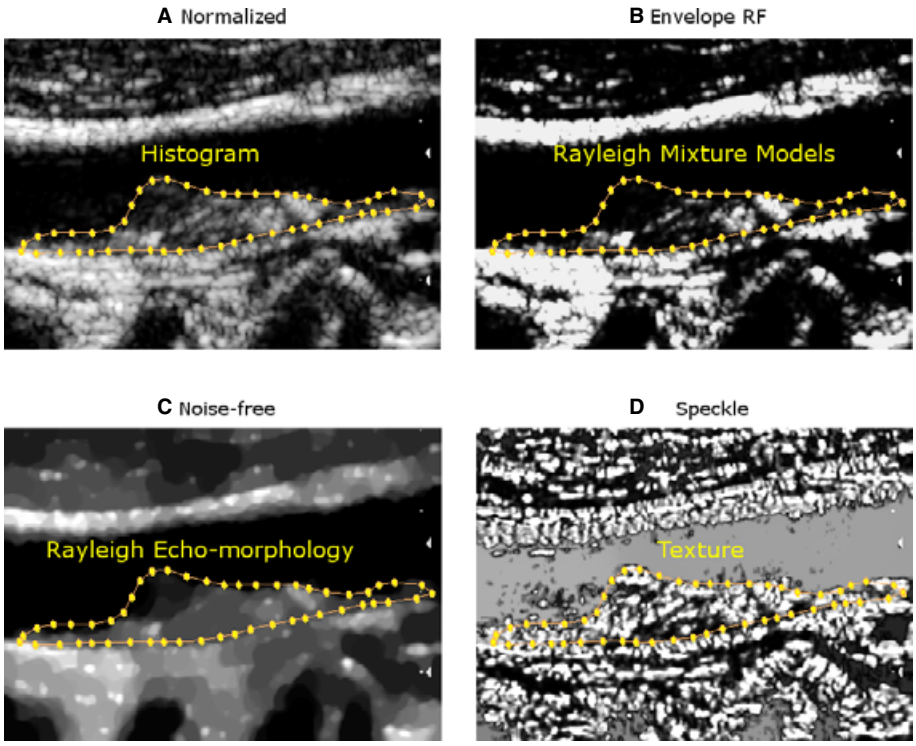

Figure 2. The computation of the enhanced activity index requires complex ultrasound image processing operations, resulting in: **A**. normalized, **B**. envelope radiofrequency (RF), **C**. noise-free, and **D**. speckle images,[35] obtained from a B-mode image. Ultrasound parameters of different type are computed from each processed image.

TABLE I

Population Characteristics

	Symptomatic	Asymptomatic	P-value
Patients			
N	30	69	
♀	7	27	0.275
♂	23	52	
Age ($\bar{x}$)	67.5	68.6	0.573
Plaques			
N	44	102	
TIA	15		
Minor stroke	10		
Major Stroke	17		
AF	2		
Degree of stenosis			
$\bar{x}$	81.3	61.9	2.78×10^{-8}
>70%	35	40	7.69×10^{-6}
50–69%	7	29	0.107
<50%	2	33	3.05×10^{-4}
Texture			
Homogenous	13	74	1.81×10^{-6}
Heterogenous	31	28	

TIA = transient ischemic accident; AF = amaurosis fugax.

Appendix A. Figure 4 shows the ROC curve obtained with the EAI. The proposed marker yields an area under curve (AUC) of 0.868 (95% CI [0.791; 0.891], P-value <0.0001). This value is comparatively higher than the values obtained with the AI and degree of stenosis curves, 0.831 (95% CI [0.726; 0.86], P-value <0.0001) and 0.828 (95% CI [0.747; 0.855], P-value <0.0001), respectively (P-values <0.0001). The higher value of AUC obtained for the EAI curve suggests a better trade-off between true positive and false positive (FP) rates when the score is used as a decision making criterion. It also indicates that a diagnosis decision based on the EAI is globally more powerful than the other investigated markers regardless of the cutoff selected.

Benchmark of EAI-Based Classification Against Degree of Stenosis and AI:

According to the empirical rule described in Appendix B, the optimal cutoffs for the degree of stenosis, AI, and EAI are 80, 65, and 55, respectively. These cutoffs can be used to design a binary classifier based on simple thresholding. Table III shows that the decision criterion based on the EAI outperforms the other markers as far as the diagnostic performance is concerned. All the studied classification performance criteria

TABLE II

Optimal Feature Set Determining the Ultrasound Profile of the Active Plaque and Used for Computing the Enhanced Activity Index

Feature	Source	P-value
Plaque disruption	Morphology	$P < 0.001$
Presence of echogenic cap	Morphology	0.001
Degree of stenosis	Morphology	$P < 0.001$
Plaque echo structure appearance	Morphology	$P < 0.001$
Mean	Normalized histogram	0.001
Skewness	Normalized histogram	0.009
Percentile 10	Normalized histogram	0.022
Percentile 50	Normalized histogram	0.047
4th Rayleigh parameter	Envelope RMM	0.010
5th Rayleigh parameter	Envelope RMM	0.010
6th Rayleigh parameter	Envelope RMM	0.010
5th mixture component	Envelope RMM	0.004
6th mixture component	Envelope RMM	0.014
No. mixture components	Envelope RMM	0.016
GLCM homogeneity	Speckle	0.016
Wavelet decomposition energy	Speckle	0.004

GLCM = gray-level co-occurrence matrix; RMM = Rayleigh mixture model.

provided higher values for the proposed risk score, notably the precision (analogous to the positive predictive value) is approximately 5% higher than the other criteria up to 70%. This result indicates that the proposed method is able to detect most of the "active" plaques while keeping the number of FPs low. Overall, when the accuracy is considered, putting together the correct identification of the TP and TN, the EAI-based classification provides the best discrimination between symptomatic and asymptomatic plaques up to 76.9%.

Discussion:

This study proposes a new objective diagnostic score for the identification of the active carotid plaque implemented through different modules of image processing, feature extraction, and plaque classification based on HDU data. This score is easy and fast to determine as its computation runs approximately on real time on a CADx platform and requires inexpensive, widely available, and easy to obtain ultrasound data.

Characterization of the active lesion is currently carried out by using objective computer-assisted methods based on characteristics of plaque echomorphology and texture. Table IV summarizes the most recent plaque classification methods based on ultrasound data.

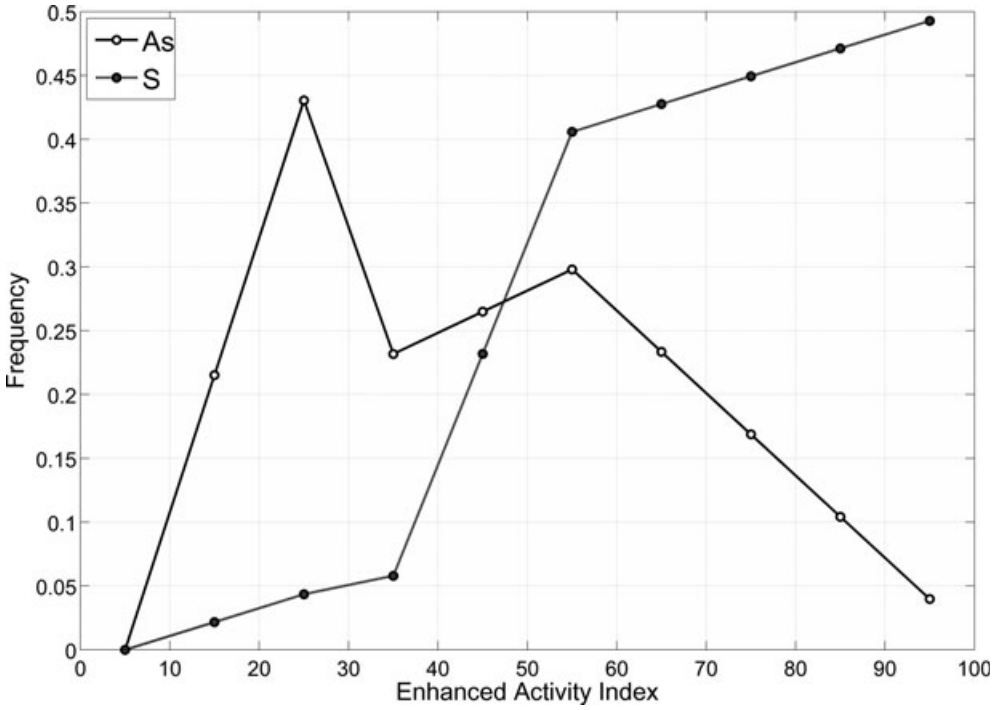

Figure 3. Distribution of plaques according to the proposed enhanced activity index.

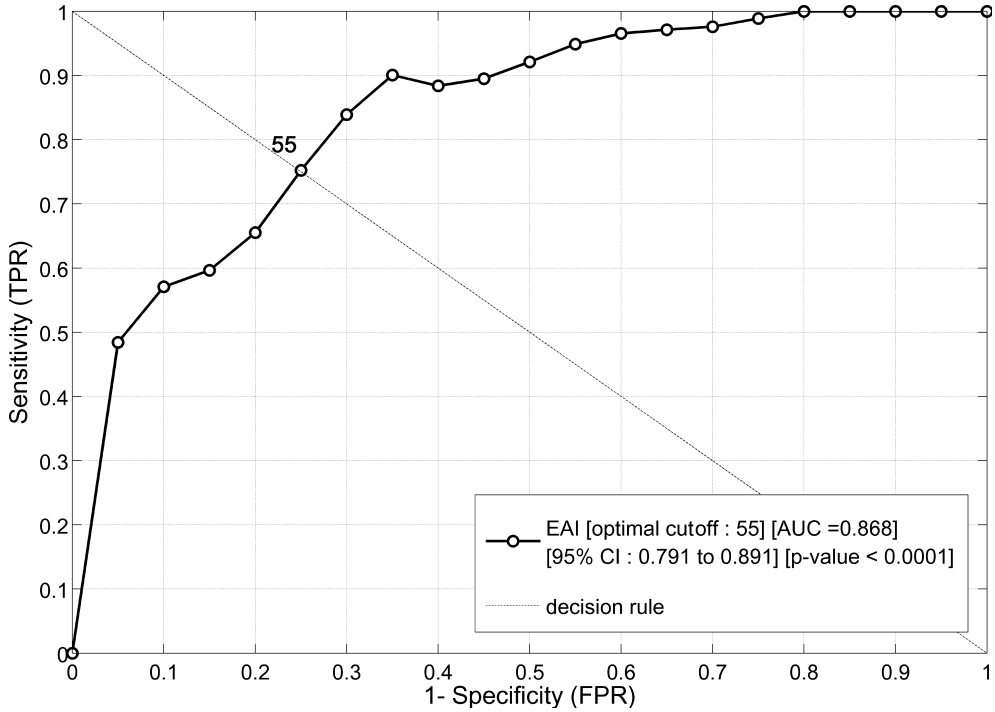

Figure 4. Receiver-operating characteristic (ROC) curve obtained with enhanced activity index. The intersection of the ROC curve with the secondary main diagonal, corresponding to equal true positive and false positive rates, is used to identify the optimal cutoff.

TABLE III

Classification Performance Results Obtained with Leave-One-Out Cross-Validation (LOOCV) for the Studied Diagnostic Based on Thresholding with Degree of Stenosis (DS), Activity Index (AI), and Enhanced Activity Index (EAI)

LOOCV (%)	DS (>80%)	AI (>65)	EAI (>55)
Accuracy	72.85	74.66	76.92
Sensitivity	67.14	65.91	70.00
Specificity	75.50	78.43	80.13
Precision	55.95	56.86	62.03

Our group has previously contributed to the concept of computer-assisted plaque analysis by introducing a score that quantifies plaque activity, combining echogenicity information from the normalized image with parameters derived from the echo structure of the entire lesion. This score, designated as AI, was associated with promising accuracy in the identification of symptomatic lesions.[17] However, it was operator dependent and prone to error based on incorrect visual interpretation of the image.

The method proposed in this study expands the AI by merging both qualitative and quantitative ultrasound criteria obtained from advanced image processing techniques. This new score is less dependent on subjective features and gives increased importance to the more objective, image-based feature space. The originality of the proposed method stands on the application of a series of ultrasound processing operations that enable to obtain a multitude of sources of information for plaque analysis from a conventional B-mode ultrasound image. A clear separation between asymptomatic and symptomatic plaques was obtained: presence of appropriate symptoms was present for scores higher than 55 on a 0 to 100 scale.

Furthermore, we compared the diagnostic yield of this new score with the early proposed AI and degree of stenosis on a cross-sectional study. We show that the EAI leads to better identification of symptomatic plaques while reducing the number of FPs.

We shall point out that this diagnostic yield is obtained with a simple classifier based on estimating the cutoff points from the ROC curve analysis (process of classification based on cutoff or thresholds). This strategy was followed in favor of other more complex classifiers because it is a method well established in the medical community and it eases the comparison with other diagnostic methods, notably the one based on the degree of stenosis. Hence, the application of more powerful classification strategies such as

TABLE IV

Summary of Plaque Characterization Methods Based on Ultrasound Images

Authors`	Material	Method	Diagnostic Yield
Madycki et al.[27]	76 plaques (17 with postoperative lesions seen on MRI)	Digital plaque texture analysis	Correlation of microembolism and incidence of silent brain infarcts (P = 0.028)
Christodoulou et al.[16]	230 plaques (115 symptomatic, 115 asymptomatic) from 209 patients	Texture features used in a modular neural network composed of self-organizing map classifiers[41]	73.1% average accuracy
Asvestas et al.[28]	10 symptomatic and 9 asymptomatic plaques	Fractal dimension of plaques estimated using the K-nearest neighbors	Fractal dimension significantly lower in asymptomatic patients (P value <0.01)
Mougiakakou et al.[18]	54 symptomatic and 54 asymptomatic plaques	Statistical and Laws' texture features employed with genetic classification algorithms	99.1% average accuracy
Kyriacou et al.[19]	137 symptomatic and 137 asymptomatic plaques	Multilevel binary and gray scale morphological features used with Probabilistic Neural Network (PNN) and the Support Vector Machine (SVM)	73.7% average accuracy
Tsiaparas et al.[29]	11 symptomatic and 9 asymptomatic	Directional multiscale textural features used with the SVM classifiers	Max. accuracy was 84.9%
Suri et al.[30–32]	44 symptomatic and 102 asymptomatic plaques	Atheromatic™ system combining discrete wavelet transform, higher order spectra and textural features using support vector machine (SVM) classifiers	Average accuracy of 91.7%
Wijeyaratne et al.[33]	74 plaques (33 asymptomatic and 41 symptomatic)	Multiple cross-sectional analysis of plaque GSM and GSM heterogeneity	Correlation of plaque echolucency (P = 0.002) and heterogeneity (P = 0.0001) with plaque symptoms

Support Vector Machines or Adaptive Boosting will improve the diagnostic yield.[25] Moreover, the fact that we propose a classification strategy based on a risk score presents an advantage among other methods described in literature: we are not limited to a binary decision, but we also provide an objective measure that quantifies the plaque activity and consequently the risk of stroke. This measure can be used by doctors in daily diagnosis.

In spite of all advantages, we do see that there is a clear scope of improvement in this study due to a small studied database. We intend to grow the plaque database over time and further validate these robust results. The current database, however, clearly demonstrates that new index correlates well with the presence of symptoms in carotid plaques.

Conclusions:

Enhanced AI is a useful diagnostic marker that correlates with carotid plaque activity expressed by the presence of appropriate neurological symptoms.

This new index is more reliable and objective than previously described AI because it combines multimodal data (clinical, echogenicity, and texture) from ultrasound images and a Bayes likelihood symptomatic/asymptomatic ratio. It is also more accurate as it provides better identification of symptomatic plaques while reducing significantly the number of FPs.

The proposed EAI, implemented in a computer-aided diagnosis platform based on ultrasound data, represents a fast, objective, and accurate descriptor of plaque activity and correlates well with clinical presentation.

Acknowledgments: Luís Mendes Pedro conducted the research, performed clinical evaluation, data collection, and all the ultrasound exams. J. Miguel Sanches introduced the algorithm for mathematical analysis. José Seabra developed and implemented the algorithms. Later, he conducted the quantitative evaluation in the cross-sectional study. Jasjit S.

Suri was instrumental in designing the manuscript and envisioning the importance of plaque characterization via image analysis for presentation to the Stroke community. J. Fernandes e Fernandes worked on the overall research planning and reviewing of the manuscript.

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Appendix A

Enhanced Activity Index:

The enhanced activity index is obtained from clinical and ultrasound parameters computed from carotid longitudinal images. In a clinical setting, the operator does not have access to the radiofrequency (RF) data so he is limited to the use of the B-mode image whose characteristics are changed by the equipment's inherent preprocessing operations. To overcome this problem, we have proposed a method to estimate the envelope RF ultrasound image.[26] In addition, a despeckling[26] method is applied to the envelope image aiming at separating the noise-free and speckle components. The noise-free image accounts for plaque echomorphology, i.e., the distribution of intensities throughout the plaque, whereas the speckle image describes how the echogenic contents are spatially arranged.

The overall procedure for image processing and feature extraction is described in detail in.[25] In short, it involves the extraction of: (i) histogram features such as mean, median, P40, standard deviation, kurtosis, skewness, energy, entropy and percentile 10, 25, 50, 75, 90 coefficients from the normalized image, (ii) parameters of the Rayleigh mixture model (RMM)[36] estimated on the envelope RF image,[34] (iii) Rayleigh statistical estimators describing echomorphology, computed from the noise-free image, and (iv) textural descriptors, such as gray-level co-occurrence matrices (GLCM), autoregressive (AR) model, and wavelet decomposition coefficients.[25] These image-based features are combined with clinical information including the degree of stenosis, evidence of plaque surface disruption or presence of fibrous cap, patient medication, risk factors, and symptomatic status. A Mann–Whitney (M-W) U hypothesis test[37] is used to select the most relevant features from a large collection of collected features. The vector $x = [x_1, x_2, \ldots, x_N]^T$ containing the N most relevant features is modeled by the following multivariate Gaussian distribution:

$$\mathrm{p}(\mathrm{x}|\mu_\tau, \Sigma_\tau) = \frac{1}{\sqrt{(2\pi)^n |\Sigma_\tau|}} \exp\left(\frac{1}{2}(x_\tau - \mu_\tau)^{\mathrm{T}} \Sigma_\tau^{-1} (x_\tau - \mu_\tau)\right) \quad \text{(A1)}$$

where μ_τ and Σ_τ are the mean and covariance matrix, respectively, of each class $\tau \in \{S, As\}$ being S and As the Symptomatic and Asymptomatic classes, respectively. The statistics μ_τ and Σ_τ are computed from the two groups of plaques. The function described in (A1) is the probability of x given the mean vector μ_τ and the covariance matrix Σ_τ, i.e., the likelihood of a given subject characterized by the feature vector x belonging to each class, S and As. The enhanced activity index is defined as follows:

$$\mathrm{EAI}(x) = G(\Gamma(x)), \quad \text{(A2)}$$

where $\Gamma(x) = \frac{R_S(x)}{R_{As}(x)}$ is called the Bayes factor,[38] $R_\tau(x) = p(x \mid \mu_\tau, \Sigma_\tau)$ is the likelihood of x with respect to class $\tau \in \{S, As\}$, and $G(x) = \frac{100}{1+\exp(1-x)}$ is a rescaling function to map the Bayes factor in the interval [0, 100]. Definition (A2) is a normalized function of the Bayes factor that quantifies the risk of a plaque to cause neurological symptoms.

The estimation of the parameters μ_τ and Σ_r in (A1) can be made from a static training set. However, to avoid a possible biased result, the computation of the activity score is made by means of the leave-one-patient-out cross-validation strategy.[39] The enhanced activity index of the ith patient is computed with (A2) using $\mu_\tau(i)$ and $\Sigma_\tau(i)$ which are in turn obtained from all the data excluding the ith patient.

Appendix B

ROC Curve Analysis:

The prediction of risk (neurologic symptoms) based on the enhanced activity index of a given patient is made according the following rule:

$$\omega = \begin{cases} S & \text{if } \mathrm{EAI}(x) > c_o \\ As & \text{otherwise} \end{cases} \quad \text{(B1)}$$

where c_o is an optimal cutoff estimated as follows. The ground-truth information about plaque condition is used to compute the sensitivity and specificity of the method for each specific value of the parameter c_o. The process is repeated for different values of c_o to obtain the receiver-operating characteristic (ROC)[40] curve where sensitivity = TN/(TN + FP); and specificity = TN/(TN + FP); TP = true positive, TN = true negative, FP = false positive, and FN = false negative. In addition, a cutoff shall be defined depending on the diagnostic decision scenario: as an example, to limit FPs (decision on surgery scenario), the optimal cutoff should be located on the left side of the coordinate axis (see Fig. 4). Here, the cutoff is chosen as the intersection of the line called "decision rule" defining equal relevance to the TP and TN (or 1 − FP) rates and the ROC curve.