Potential carotid atherosclerosis biomarkers based on ultrasound image analysis

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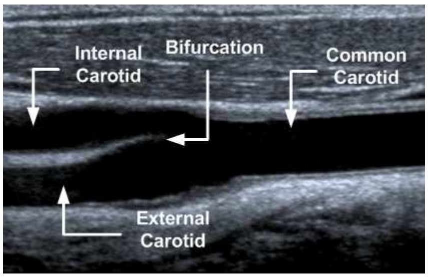
ABSTRACT
It has been shown that computerized analysis of ultrasound images of the carotid artery may provide quantitative disease biomarkers and can potentially serve as a "second opinion" in the diagnosis of carotid atherosclerosis. Extending the findings of previous work on the subject, a set of methodologies are presented in this chapter, suitable for application on two-dimensional B-mode ultrasound images. More specifically, a Hough-Transform-based technique for automatic segmentation of the arterial wall allows the estimation of the intima-media thickness and the arterial distension waveform, two widely used determinants of arterial disease. Texture features extracted from Fourier-, wavelet-, and Gabor-filter-based methods can characterize symptomatic and asymptomatic atheromatous plaque. Finally, a methodology based on least-squares optical flow is proposed for the analysis and quantification of motion of the arterial wall.
The suggested methodologies allow the extraction of useful biomarkers for the study of (a) the physiology of the arterial wall and (b) the mechanisms of carotid atherosclerosis.

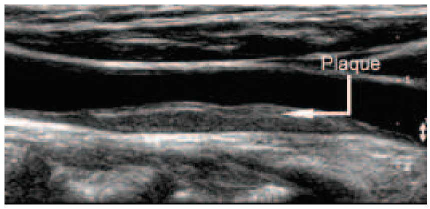
1 Introduction

The carotid arteries are responsible for supplying blood to the brain. Each common carotid artery divides into an external and an internal branch at the carotid bifurcation. The external carotids supply blood to the neck, pharynx, larynx, lower jaw and face, whereas the internal carotids enter the skull delivering blood to the brain. The presence of an atheromatous lesion, or plaque, in the carotid arteries, also known as carotid atherosclerosis, may disturb the normal circulatory supply to the brain. Carotid atherosclerosis may produce total occlusion of a specific arterial site or cause a thromboembolic event. In advanced stages of the disease, cerebrovascular symptoms, such as transient ischaemic attack, amaurosis fugax (temporal blinding) or stroke, may occur.

Ultrasound imaging of the carotid artery is the most widely used modal-



(a)



(b)

FIGURE 1. Examples of B-mode ultrasound images of (a) a healthy (non-atherosclerotic) and (b) a diseased (atherosclerotic) carotid artery.

ity in the diagnosis of carotid atherosclerosis due to its noninvasiveness, non-ionizing nature and low cost. In particular, B (Brightness)-mode imaging, i.e. the reproduction of the amplitude of the reflected waves by their brightness, is commonly used to assess arterial wall morphology. B-mode images exhibit a granular appearance, called speckle pattern, which is caused by the constructive and destructive interference of the wavelets scattered by the tissue components. In B-mode ultrasound, blood reflects very little and the vessel lumen appears as a hypoechoic band. Figure 1 shows examples of B-mode ultrasound images of (a) a healthy (non-atherosclerotic) and (b) a diseased (atherosclerotic) carotid artery.

2 Quantitative assessment of carotid atherosclerosis

Currently, severity of carotid atherosclerosis and selection of patients to be considered for endarterectomy, i.e. surgical removal of plaque, are based (a) on the degree of stenosis caused by the plaque, in asymptomatic subjects, and (b) on both the degree of stenosis and previous occurrence of clinical symptoms, in symptomatic subjects. However, there is evidence that atheromatous plaques with relatively low stenosis degree may produce symptoms and that highly stenotic atherosclerotic plaques can remain asymptomatic. Because not all carotid plaques are necessarily harmful and because carotid endarterectomy carries a considerable risk for the patient, the crucial task of optimized selection of patients for operation may be greatly facilitated by the use of novel biomarkers. B-mode ultrasonic images, in combination with appropriate image processing methods for segmentation, texture and motion analysis, may be used to extract useful diagnostic indices of the geometry, echogenicity and strain, respectively, of the carotid artery wall.

2.1 Prior Art

Previous work on computerized analysis of ultrasound images of the carotid arteries includes automatic segmentation of the arterial lumen, plaque texture analysis and tissue motion analysis. The use of deformable models [12], including snakes [3], allows automatic identification of the random-shaped carotid artery wall from static ultrasound images. In addition to this, the Hough Transform (HT) has been used to segment the arterial wall from sequences of images [15, 17]. In this case, the arterial distension waveform can be estimated facilitating the study of the dynamic arterial geometry. Plaque echogenicity, estimated from B-mode ultrasound images using texture analysis techniques, may be used to characterize atheromatous plaque and differentiate between symptomatic and asymptomatic cases. Plaque echogenicity has been analyzed using a number of statistical, model-based and Fourier-based methods [16, 4]. Motion of the arterial wall and atheromatous plaque has recently gained attention as a determinant of carotid atherosclerosis. It has been shown that plaque strain, expressed as relative motion between different parts of the plaque, may be related to plaque instability, i.e. to the risk for cerebrovascular complications, such as stroke [13]. Temporal sequences of ultrasound images can be used to estimate movement of the carotid artery wall by tracking the speckle patterns generated by the tissue [13, 7, 5].

The purpose of this chapter is to suggest a set of methodologies which extend the findings of previous work on computerized analysis of ultrasound images of the carotid artery in an attempt to identify quantitative indices of diagnostic value. Such indices may be useful for early and valid diagnosis of atherosclerosis as well as for the study of the physiology of the normal and diseased arterial wall.

3 Computerized analysis of ultrasound images of carotid artery

The methodologies described in this chapter are suitable for two-dimensional (2D) B-mode ultrasound imaging. This is the most widely used modality for the assessment of the carotid artery. The methodologies aim at (a) automatic segmentation of the arterial wall from longitudinal and transverse sections, (b) texture analysis of atheromatous plaque and (c) analysis and quantification of motion of the arterial wall. It is recommended that the methodologies be applied to normalized ultrasound images, according to widely accepted specifications [6], to minimize variability introduced by different equipment, operators and gain settings and facilitate imaged tissue comparability. The techniques are designed to be applied to sequences of images, thus allowing the extraction of quantitative information at different phases of the cardiac cycle, e.g. systole or diastole. Obviously, it is possible to apply them to individual (static) images, if this is required by the clinical application.

4 Early disease biomarkers

Early disease stages may be assessed by interrogating the arterial wall on which focal lesions (plaques) may not yet have become obvious. The suggested HT technique allows the automatic extraction of straight lines and circles to approximate the wall-lumen boundary in longitudinal and transverse sections, respectively. HT can be used to detect parametric curves of the form $v(c, p_i) = 0$ in digital images, where c is the vector of coordinates, p the vector of parameters and $i = 1...n$, the number of parameters required to define the curve. HT transforms the image to an n-dimensional parametric space, called the accumulator array. Operating on a binary image of edge pixels, all possible curves $v(c, p_i) = 0$ through a pixel with vector coordinates c are transformed to a combination of parameters p_i, which then increment the corresponding cell of the accumulator array. The main steps of the methodology, which are described in detail in [8], include:

Reduction of image area This may be achieved by automatically isolating a rectangular area containing the vessel lumen. To this end, four points may be defined to delimit the area to be investigated. This is an important step because it minimizes the possibility to detect unwanted structures, which may be present biasing the representation of the arterial lumen and, thus, reduces the computational cost and the time required to perform the segmentation task.

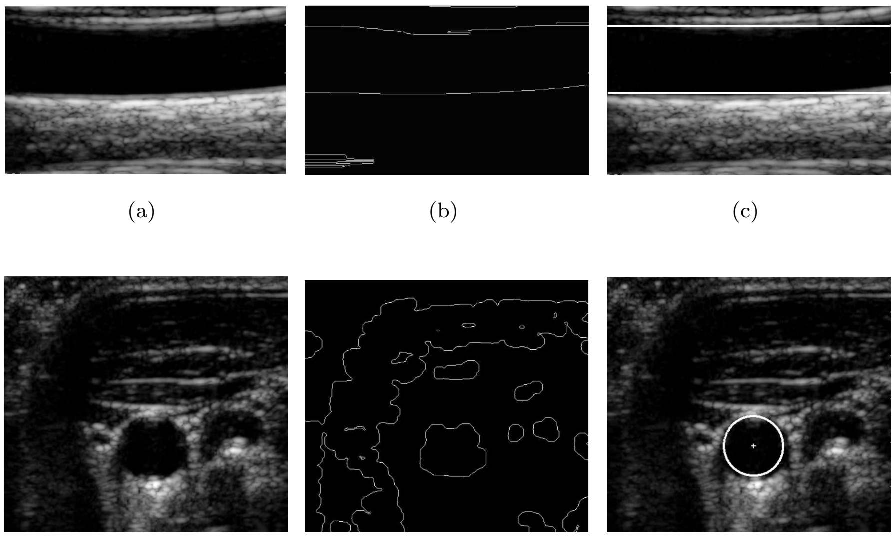
Image pre-processing This step includes removal of high frequency noise using a symmetric Gaussian lowpass filter and morphological closing to suppress small 'channels' and 'openings' of the image.

Edge detection The image is first transformed into binary through the application of a global threshold and then a Sobel gradient operator may be applied.

Hough Transform Longitudinal sections are searched for lines defined as $z = xcos\theta + ysin\theta$, where z is the distance from the left upper corner of the image and θ is the angle with the x-axis. Transverse sections are searched for circles defined as $(x-a)^2 + (y-b)^2 = r^2$, where (a, b) are the coordinates of the center and r is the radius of the circle.

Selection of dominant lines/circle Two lines in longitudinal sections and one circle in transverse sections with the maximal values in the corresponding accumulator arrays are eventually selected, representing the boundaries of the wall-lumen interface.

Figure 2 shows examples of the application of the HT technique in longitudinal and transverse sections of ultrasound images of the carotid artery. Arterial diameters can be calculated through the application of the pre-



(a) (b) (c)

(d) (e) (f)

FIGURE 2. Examples of the application of the HT technique in longitudinal and transverse sections of ultrasound images of the carotid artery. (a), (d) original images, (b), (e) images after morphological closing, thresholding and edge detection. (c), (f) HT technique result shown on original image.

viously described methodology, namely from the distance of the two lines in longitudinal sections and the circle diameter in transverse sections. The arterial distension waveform can then easily be estimated by recording the diameter values in all images of the sequences. Furthermore, in longitudinal sections, the HT methodology can be applied to the far wall alone, to extract two dominant lines corresponding to the boundaries of the wall, from which the intima-media thickness can be evaluated.

A methodology combining HT and active contours is also suggested, in an attempt to achieve a more accurate approximation of the arterial wall geometry in transverse sections. Departure from the strict geometrical shape indicated by HT is more evident in these sections. The methodology is based on the generation of a gradient vector flow field [18], an approach attempting to overcome conventional active contours constraints. The main steps include:

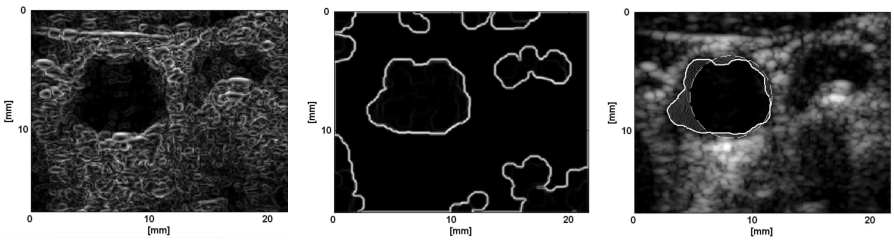
HT technique Application of the HT methodology described above allows the estimation of a circle, which is subsequently used for initializing the active contour.

Image pre-processing This step includes a number of tasks (calculation of gradient field, thresholding, morphological closing and smoothing, and gradient operator application) to estimate the image edge map.

Calculation of gradient vector flow field

Contour estimation Deformation of initial curve (circle) based on gradient vector flow field.

Figure 3 shows an example of the application of the combined HT-active-contours methodology in a transverse section of the carotid artery. As we can see, the methodology results in a random shaped boundary which follows more closely the actual wall-lumen interface than the circle. However, widely used physiological indices, such as the arterial distension waveform, may be more easily estimated from the latter.



(a) (b) (c)

FIGURE 3. Examples of the application of the combined HT-active-contours technique in a transverse section of the carotid artery. (a) illustration of gradient field of original image. (b) image after application of gradient operator on gradient field . (c) combined HT-active-contours methodology result shown on original image (solid line); dashed line indicates result (circle) of HT methodology.

5 Assessment of advanced stages of disease

The severity of the carotid atherosclerotic plaque, an advanced disease stage, can be assessed through its echogenicity estimated by a number of texture analysis techniques. The use of transform-based texture analysis is suggested here, which has not been previously applied in ultrasound images of the carotid artery. The Fourier Transform (FT), the Wavelet Transform (WT) and Gabor filters allow the estimation of texture features capable of characterizing symptomatic and asymptomatic plaques.

The discrete 2D FT [9] can be used to quantify image texture in the frequency domain. The radial distribution of values in Fourier Power Spectrum (FPS) is sensitive to texture coarseness in an image, whereas their angular distribution is sensitive to the directionality of the texture. Power concentration in low spatial frequencies indicates coarse texture, while power concentration in high frequencies indicates fine texture. Texture with strong directional characteristics produces a power spectrum concentrated along lines perpendicular to the texture direction. A total of nine texture features can be extracted from the FPS, five corresponding to the radial and four to the angular distribution of the FPS.

The 2D WT can be used to analyze the frequency content of an image within different scales [1] and, thus, to extract information about the low and high frequencies of an image at different resolutions. The resulting wavelet coefficients are called the sub-images at different resolutions and consist of an approximation image and three detail images, namely the horizontal, vertical and diagonal detail images. Quantitative texture measures can be extracted from the wavelet coefficients. Each plaque image can be decomposed up to five scales using an orthogonal, near symmetric and compactly supported mother wavelet, the symlet20 [2]. The choice of the mother wavelet is critical and, because the interrogated images exhibit rapid intensity fluctuations, a tight wavelet should be preferred. We suggest avoiding the use of the approximation sub-images for texture analysis because they represent a rough estimate of the original image and capture variations induced by lighting and illumination. A total of one hundred features can be extracted for each plaque image based on this methodology.

Gabor filters are a group of wavelets. They can be obtained by the dilation and rotation of a Gaussian function modulated by a complex sinusoid. A set of filtered images can be obtained by convolving Gabor filters with the original plaque image. Each of these filtered images represents texture information of the image at a specific scale and orientation. From each filtered image two features, namely the mean and standard deviation of the magnitude of the transformed coefficients, can be extracted [10]. These represent the energy content at different scales and orientations of the image. We suggest using five scales and four orientations resulting in a total of twenty Gabor-based texture features.

6 Motion analysis of normal and diseased arterial wall

To address the problem of arterial wall motion estimation, a methodology based on weighted least-squares optical flow (WLSOF) [11] is suggested. Compared to conventional optical flow, which was previously used in similar applications [13, 14], WLSOF allows smoothing out of large velocity differences between adjacent sites. WLSOF is used to recover velocity from the following equation, known as the gradient constraint equation relating velocity to the space and time derivatives at any one point of the image:

$$\mathbf{u} \cdot \nabla I(\mathbf{x}, t) + I_t(\mathbf{x}, t) = 0$$

where $\mathbf{u} = \frac{\Delta u}{\Delta t} = (u_x, u_y)$, and $\nabla I(\mathbf{x}, t)$ and I_t denote spatial and temporal partial derivatives, respectively, of the image I.

A common way to constrain velocity is to use gradient constraints from neighboring pixels, assuming that they share the same 2D velocity. In reality, there may be no single velocity value that simultaneously satisfies all pixels of the region, so the velocity that minimizes the constraint errors is found instead. The least-squares estimator that minimizes the squared errors is:

$$E(\mathbf{u}) = \sum_{\mathbf{x}} g(\mathbf{x}) \cdot [\mathbf{u} \cdot \nabla I(\mathbf{x}, t) + I_t(\mathbf{x}, t)]^2$$

where $g(\mathbf{x})$ is a Gaussian weighted function. It is used to enhance constraints in the center of the neighborhood, thus increasing their influence. The minimum of $E(\mathbf{u})$ can be found from the critical points, where derivatives with respect to $\mathbf{u}$ are equal to zero:

$$\frac{\vartheta E(\mathbf{u})}{\vartheta u_x} = \sum_{\mathbf{x}} g(\mathbf{x}) \cdot [u_x \cdot I_x^2 + u_y \cdot I_x \cdot I_y + I_x \cdot I_t]$$

$$\frac{\vartheta E(\mathbf{u})}{\vartheta u_y} = \sum_{\mathbf{x}} g(\mathbf{x}) \cdot [u_y \cdot I_y^2 + u_x \cdot I_x \cdot I_y + I_y \cdot I_t]$$

The above equations can be written in matrix form and the resulting linear system can be solved using the Gaussian elimination method.

To compute spatial (I_x, I_y) and temporal (I_t) gradients, the images can first be smoothed using a Gaussian 7×7 kernel with standard deviation 0.8. Use of the Gaussian lowpass filter also allows removal of high frequency noise inherent in ultrasound images.

To estimate arterial wall motion, the previous method can be applied to appropriately selected image areas. These include pixels of the normal and/or diseased wall and exclude pixels of the lumen and the surrounding tissue. Specifically, pixels at a distance of 1.5 mm along the interface, i.e. in the longitudinal direction, and at a distance of 0.5 mm through the tissue, i.e. in the radial direction, can be selected. Pixel density is lower in the longitudinal direction because less relative motion is expected compared to the radial direction. Reduction of the image area to a set of individual pixels for further investigation reduces significantly the computational cost without compromising the related physiological information.

Figure 4 shows examples of velocity fields of the far arterial wall of a normal artery, as well as for a symptomatic and an asymptomatic case. In the same figure, examples of longitudinal and radial displacement waveforms for two points on the wall are also shown. The points distance is approximately 12.5 mm; in the case of the diseased (atherosclerotic) wall one point is on the plaque and the other on the adjacent normal part of the wall. As we can see, axial displacement, i.e. displacement along the arterial wall, exhibits a periodic pattern of frequency equal to almost double the frequency of the radial displacement. This finding agrees with recently reported results [5].

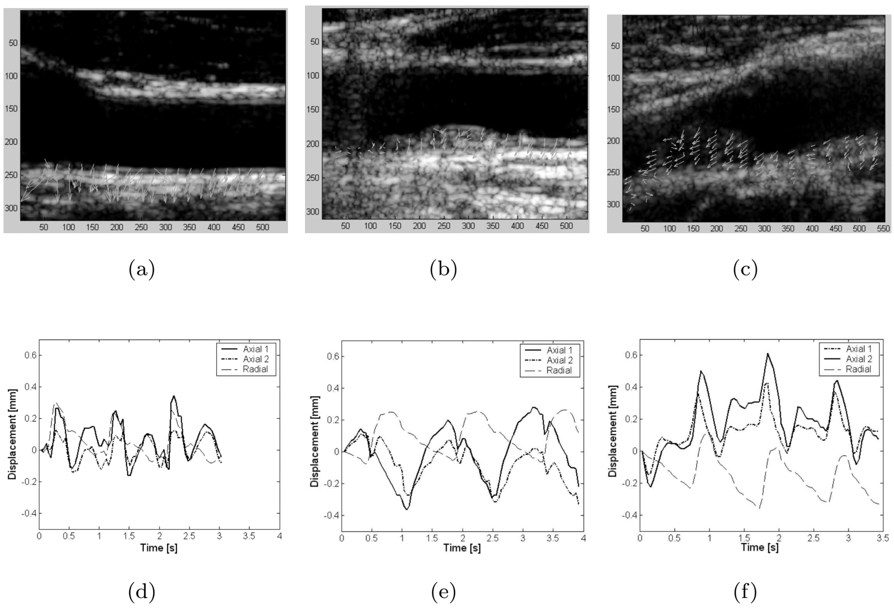


FIGURE 4. Examples of velocity fields and displacement waveforms obtained by the application of the WLSOF methodology in a healthy (non-atherosclerotic) arterial wall (a, d), an asymptomatic plaque (b, e) and a symptomatic plaque (c, f). Illustrated vectors were enhanced by a factor of 10. Velocities correspond to beginning of systole.

7 Experimental results and discussion

The methodologies presented here are useful for the quantitative assessment of carotid atherosclerosis. In combination with the experience of a specialized physician, they may improve the diagnostic power of ultrasound imaging. Their integration into clinical practice depends not only on their performance but also on how well the physician performs a task when the computer output is used as an aid.

More specifically, the suggested HT technique provides a simple, fast and accurate way to identify the arterial wall in longitudinal and transverse sections of the carotid artery and can be used in clinical practice to estimate indices of arterial wall physiology, such as the IMT and the ADW. In ten normal subjects, the specificity and accuracy of HT-based segmentation were on average higher than 0.96 for both sections, whereas the sensitivity was higher than 0.96 in longitudinal and higher than 0.82 in transverse sections. The corresponding validation parameters for IMT estimation were generally higher than 0.90. The HT technique was also applied to 4 subjects with atherosclerosis, in which sensitivity, specificity and accuracy were comparable to those of normal subjects; the low values of sensitivity in transverse sections may reflect departure from the circular model due to the presence of plaque. For these cases, the combined HT-active-contours technique was found to increase the sensitivity values.

Texture features using the three transform-based methods described previously were extracted from a limited number of symptomatic (ten plaques) and asymptomatic (nine plaques) cases. Differences between the two case types were estimated using bootstrapping. Both the WT- and the Gabor-filter-based methodologies resulted in significantly different features, which characterized texture at low resolutions and in the horizontal direction. Features at low resolutions are indicative of fine texture; finer texture was found in symptomatic compared to asymptomatic plaques. Horizontal texture patterns are an interesting finding, especially when one combines this information with arterial wall biomechanics. Mechanical stresses due to blood blow may be responsible for such texture patterns; compared to blood pressure, the other main cause of stress on the arterial wall, the effect of blood flow is more pronounced around a plaque. The discriminative ability of the transform-based texture features was found superior to that of the gray-scale median, a widely used texture parameter of carotid plaque, for the small population that was interrogated, emphasizing the need for using advanced techniques to efficiently characterize atheromatous plaque.

Reliable estimation of arterial wall motion is a challenging task and is believed to provide a powerful tool in the study of the physiology and biomechanics of atheromatous plaque. The strain experienced by the arterial wall is a crucial biomarker of carotid atherosclerosis and can be assessed through motion analysis. In combination with information of the exerted stresses, it can prove useful for the study of the mechanical behavior of cardiovascular tissue.

8 Conclusion

The methodologies presented in this chapter are expected to provide powerful tools in the diagnosis of carotid atherosclerosis because they can assist interpretation of ultrasound images. Individual techniques facilitate the diagnostic tasks of vessel wall identification, plaque characterization and strain estimation of normal and diseased arterial wall.

9 References

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