Toward Novel Noninvasive and Low-Cost Markers for Predicting Strokes in Asymptomatic Carotid Atherosclerosis: The Role of Ultrasound Image Analysis

Spyretta Golemati, *Member, IEEE*, Aimilia Gastounioti, *Student Member, IEEE*, and Konstantina S. Nikita*, *Senior Member, IEEE*

***Abstract*—Stroke is a serious and frequent cerebrovascular disease with an enormous socioeconomic burden worldwide. Stroke prevention includes treatment of carotid atherosclerosis, the most common underlying cause of stroke, according to a specific diagnostic algorithm. However, this diagnostic algorithm has proved insufficient for a large number of mostly asymptomatic subjects, which poses a significant research challenge of identifying novel personalized risk markers for the disease. This paper illustrates the potential of carotid ultrasound image analysis toward this direction, with ultrasound imaging being a low-cost and noninvasive imaging modality and ultrasound-image-based features revealing valuable information on plaque composition and stability. A concise report of state-of-the-art studies in the field is provided and a perspective for clinical scenario for optimal management of atherosclerotic patients is described. Challenges and necessary future steps toward the realization of this scenario are discussed in an attempt to urge and orient future research, and mainly include systematic applications to sufficiently large patient samples, appropriately designed longitudinal studies, confirmation with histological results, and clinical trials.**

***Index Terms*—Carotid, image analysis, stroke, ultrasound.**

I. Introduction

STROKE is a serious cerebrovascular disease and accounts for the third most common cause of death in developed countries exceeded only by coronary artery disease and cancer. Stroke is an acute manifestation of atherosclerosis and consists in brain tissue damage due to interrupted blood supply to the brain. Of the 15 million people suffering a stroke annually, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community [1]. Reported prevalence rates range from 5% in subjects aged less than 75 years to 10% or more in subjects aged more than 80 years in Europe [2] and are about 3% in the USA [3]. Projections show a 24.9% increase in prevalence from 2010, by 2030 [3]. Stroke burden is projected to rise from around 38 million disability-adjusted life years (DALYs) globally in 1990 to 61 million DALYs in 2020 [1]. Although the incidence of stroke is declining in high-income countries, it is increasing in middle- and low-income countries [4]; furthermore, the absolute number of strokes continues to increase because of the aging population.

An international comparison of stroke cost studies showed that, on average, 0.27% of gross domestic product was spent on stroke by national health systems, and stroke care accounted for about 3% of total health care expenditures [5]. Accordingly, it can easily be argued that the economic burden of stroke is requiring increasing attention for more effective health care planning and allocation of resources.

Carotid atherosclerosis (CA) is the underlying cause of the majority of strokes. In its asymptomatic status, in particular, it is increasingly encountered in the general clinical practice, as a result of increased life expectancy as well as easier disease detection due to advances in medical imaging. CA is a manifestation of the systemic atherosclerotic disease, in which fatty deposits, inflammation, cells, and scar tissue build up within the walls of arteries. The presence of stenotic plaques, causing luminal narrowing of more than 50% in internal carotid arteries, is positively associated with a higher incidence of ischemic events, i.e., strokes, in the elderly [6].

Ultrasound imaging holds a prominent position in the diagnosis of CA. Compared to other imaging modalities, namely magnetic resonance imaging, computed tomography, and nuclear imaging, which allow accurate identification and evaluation of vessels [7], ultrasound has a number of advantages, including noninvasiveness, widespread availability, short examination times, lack of radiation exposure, and low cost. Such advantages have established it as a validated method for visualizing and quantifying atherosclerotic lesions using a repeatable procedure that has proved to be a strong indicator of cardiovascular disease. It is also the best means for follow up. Ultrasound imaging shows some limitations in the detection of carotid

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S. Golemati is with the National Kapodistrian University of Athens, Athens 106 79, Greece (e-mail: sgolemati@med.uoa.gr).

A. Gastounioti is with the School of Electrical and Computer Engineering, National Technical University of Athens, Athens 106 80, Greece (e-mail: gaimilia@biosim.ntua.gr).

*K. S. Nikita is with the School of Electrical and Computer Engineering, National Technical University of Athens, Athens 106 80, Greece (e-mail: knikita@ece.ntua.gr).

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stenosis due to the required high operator skill and experience, and the large interpersonal variability [8].

Following ultrasound evaluation, as well as clinical examination, a decision is made for appropriate treatment of CA. However, the existing "one-size-fits-all" treatment algorithm has been shown to be inadequate and inefficient, especially in terms of patient safety and cost effectiveness [9]. This issue is discussed in more detail in Section II. Therefore, there is an ultimately important clinical challenge, namely, to accurately and objectively identify CA patients at high-, intermediate- and low-risk for stroke and offer them the appropriate treatment. Such challenge is eventually "projected" to an engineering- and technology-based challenge, consisting in recruiting state-of-the-art methods for image analysis, and optimizing them toward identifying early, valid and personalized risk markers, and refining the current diagnostic-decision-making algorithm.

The purpose of this paper is to put into the appropriate perspective the crucial issue of early stroke prediction using ultrasound image analysis (UIA). To this end, the challenge that faces the scientific community is clearly outlined in Section II and a concise report of state-of-the-art methods for carotid UIA is provided in Section III. Subsequently, the valuable consultation roles of automatic classification and efficient management of the collected data in the context of a perspective for clinical scenario are described in Section IV. Finally, Section V highlights the required future steps in this continuously evolving field of interdisciplinary research toward the realization of the presented clinical scenario. This paper concludes in Section VI.

II. Challenge: Valid Diagnosis of Carotid Atherosclerosis and Risk Stratification

Among the subjects suffering from CA, some are more likely to experience cerebrovascular symptoms than others. Those at high stroke risk have atheromatous plaques known as "vulnerable plaques". Although plaque vulnerability has been addressed in a number of studies, a formal definition of this term is still lacking; proposed definition criteria have included active inflammation, a thin cap with a large lipid core, endothelial denudation, fissured cap, severe stenosis, or combinations of these findings [10]. Early and valid discrimination between vulnerable and stable carotid plaques is critical for optimal management of the disease.

Diagnosis and monitoring of CA are currently based on the degree of stenosis, i.e., the percentage of lumen area occupied by atheromatous material. The degree of stenosis is estimated ultrasonographically, using B-mode and Doppler and taking into account systolic and diastolic velocity peaks [8]. In current clinical practice, asymptomatic subjects with stenosis degrees higher than 70% are offered an invasive revascularization procedure (endarterectomy or stenting), whereas subjects with lower stenosis degrees are not; both groups are offered medical treatment, namely statin therapy [see Fig. 1(a)]. Patients with asymptomatic carotid stenosis $\geq$50% have an overall risk of stroke 2% per year and within this patient group higher stenosis degrees are associated with higher risk [11]. Selecting the appropriate asymptomatic subject for intervention remains a considerable dilemma in disease management for the treating physician. Symptomatic subjects with degrees of stenosis larger than 50% are all offered a revascularization procedure [12]. It is pointed out that a subject is considered asymptomatic if they have not experienced a cerebrovascular symptom within a specific time period, usually not longer than six months, prior to the time of the examination.

Although the degree of stenosis has traditionally been approved as a key point laboratory measurement for the therapeutic decision making of CA, several studies have indicated that most cerebrovascular events are associated with less severe stenosis, and plaque composition appears to be a critical determinant of the risk for future ischemic events [13]. The surgical procedure itself also holds risks for patient safety [14]. In addition to this, it has recently been shown that 94% of all carotid revascularization procedures in asymptomatic patients in the US are ultimately unnecessary, costing health-care providers US$2 billion annually [9].

Based on the aforementioned, and given the substantial socioeconomic cost of the disease and its potential adverse clinical events as well as the risk to patient safety related to the available therapeutic options, there is an undoubted clinical need to better identify those asymptomatic subjects with vulnerable plaques, i.e. at high risk of stroke, who really need a surgical intervention to prevent cerebrovascular events, and spare those with stable plaques from potentially unnecessary and harmful interventions.

The importance of this clinical challenge is highlighted not only in isolated single-center studies, but also in multicentre collaborative projects. The BioImage study aims to evaluate associations among imaging and circulating biomarkers and their ability to predict atherothrombotic events in asymptomatic at-risk subjects in the primary prevention of myocardial infarction and stroke [15]. Recently, a full model for atherosclerotic plaque formation and development was presented as part of ARTreat Project [16], which aims at providing a patient-specific computational model to improve the prediction quality for CA progression and risk.

As a step forward, the capabilities offered by the widely used ultrasound imaging can be combined with advanced methods for UIA, which allow the in-depth investigation of morphological and mechanical properties of arterial segments. The incorporation of the extracted information in classification schemes may eventually lead to "intelligent" diagnostic tools, which, along with efficient data management, will personalize and improve disease management.

III. State of the Art: Characterization of Carotid Atherosclerosis

Current clinical decision making in terms of treating the asymptomatic CA is now mitigated by multiple factors beyond the ultrasonographically determined degree of stenosis, the presence of symptoms and clinical familial history. Furthermore, recent advances in computerized methods for UIA have allowed the extraction of features for describing tissue echogenicity/texture, motion/elasticity, and morphology, thus

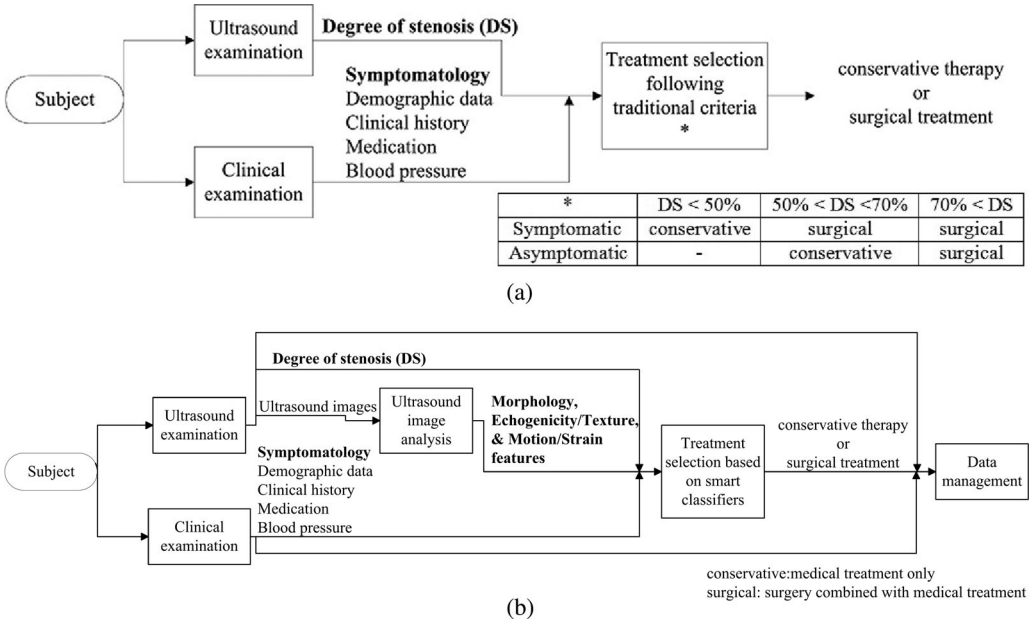

Fig. 1. Graphical representation of (a) current diagnostic algorithm and (b) a scenario for a future, refined, algorithm, for management of carotid atherosclerosis. Boldface indicates the features used for treatment selection in each case.

providing additional information on plaque composition and stability. The usefulness of such measures in enhancing the diagnostic procedure lies in their potential ability to discriminate between vulnerable and stable plaques as well as to characterize tissue modifications following specific therapeutic procedures. In the following paragraphs, the state-of-the-art research in these areas is briefly described.

A. *Echogenicity and Texture Analysis*

The allocation of echogenic (fibrous and calcified tissue) and anechoic (blood, lipids) materials within the plaque determines the appearance and spatial distribution of gray levels in plaque ultrasound images, which can be quantified using image echogenicity and texture analysis, respectively. A number of studies have compared symptomatic and asymptomatic cases in terms of their echogenicity and texture characteristics. In this context, plaque echogenicity has been analyzed with various statistical methods ([17], [18]), among which the gray scale median (GSM) has been extensively used in the study of different aspects of vascular disease. According to these studies, low GSM values, corresponding to echolucent plaques, have been associated with symptomatic cases, and are therefore considered as indices of vulnerable plaque. More advanced texture analysis methods, based on multiresolution and multiscale texture analysis, can be more efficient than statistical measures in discriminating symptomatic and asymptomatic plaques [19], [20]. An interesting finding, in the case of wavelet-based analysis, was that the dominant texture features exhibited horizontal directionality, suggesting that texture may be affected by biomechanical factors (plaque strains) [19]. In a recent study, it was shown that statistical and spectral features were more sensitive to statin-related changes in CA than plaque volume [21].

As opposed to the previous cross-sectional studies, longitudinal studies, including follow-up procedures, are rather limited; a recent one has shown that a combination of plaque echogenicity and embolic signals can facilitate stratification of risk of stroke [22]. An integrated plaque risk score, defined as a combination of stenosis degree, plaque surface irregularity, echogenicity, and texture, was also suggested as a more powerful predictor of cerebrovascular events, compared to the traditional Framingham score [23]. The crucial issue of validation, including comparison with histological samples, has only been investigated in a few studies ([17], [24]).

In an attempt to understand the significance of echogenicity-based features, these have been associated with biochemical markers implicated in plaque destabilization and rupture. Echolucent plaques have been associated with elevated levels of triglyceride-rich lipoproteins, lower levels of high-density-lipoprotein cholesterol [25], elevated plasma concentrations of the acute phase reactants orosomucoid, interleukin-6 and high sensitivity c-reactive protein [26], and circulating oxidized low-density lipoprotein [27].

B. *Motion Analysis*

Dynamic B-mode ultrasound imaging of longitudinal sections of the arterial wall allows the estimation of tissue motion in two dimensions, namely longitudinal, i.e., along the vessel axis, and radial, i.e., along the vessel radius, and perpendicular to the longitudinal one. Radial displacements of the arterial wall have been extensively studied and adequately correlated to a number of cardiovascular diseases [28]. On the other hand, studies interrogating the longitudinal direction have relatively recently emerged, and have shown the usefulness of this motion component. The analysis of motion of normal common carotid artery segments in healthy individuals has revealed a significant

longitudinal component of wall strain comparable, and sometimes larger, in magnitude to the radial component [29], [30]. The longitudinal displacement patterns of the arterial wall have been found significantly different among healthy subjects of similar ages and genders but constant within subjects interrogated at two time instances four months apart [31].

Wall displacements of nonatherosclerotic common carotid artery areas have also been measured in subjects with diabetes [32], coronary artery disease [33], periodontal disease [34], and carotid plaque [35]. All studies reported impaired arterial tissue movements in the presence of disease.

The investigation of motion of the carotid atherosclerotic plaque is more challenging than that of the normal wall because the local geometry is more complicated and arterial borders appear fuzzier; it is also much more clinically interesting. Therefore, only a few studies have associated motion patterns of the plaque with the risk for cerebrovascular complications, such as strokes or transient ischaemic attacks [36]. In one of the first studies on plaque motion analysis, asymptomatic plaques had surface motion vectors of equal orientation and magnitude to those of the internal carotid artery, whereas symptomatic plaques demonstrated evidence of inherent plaque movement [36]. Maximal surface velocity was not different between the two plaque types, but maximal discrepant velocity, defined as the maximal difference between maximal and minimal velocities, was significantly higher in symptomatic plaques [36]. Preliminary results of later studies suggested that parameters describing tensional and torsional plaque motion [37] and motion-based strain imaging methods [38], [39] may be able to discriminate vulnerable plaques.

Imaging tissue displacements and strains (see Fig. 2) allows better visualization of biomechanical patterns, which may account for plaque rupture or fissures. Recently, it was shown that heterogeneous material composition of the plaque reduces its movement in both motion directions, probably because of interactions between different materials [40]. Furthermore, echogenic image regions moved more intensely in the longitudinal direction than anechoic image regions, while the opposite was observed for the radial direction (see Fig. 3).

An important part of ongoing research focuses on improving existing methods in terms of accuracy in motion tracking. Kalman filtering [41], multiscale motion analysis [42] and weighted-least-squares optical flow [43] have been shown to outperform the more conventional block matching technique. Such methods may be promising for addressing challenging issues, including tracking of fuzzy arterial borders.

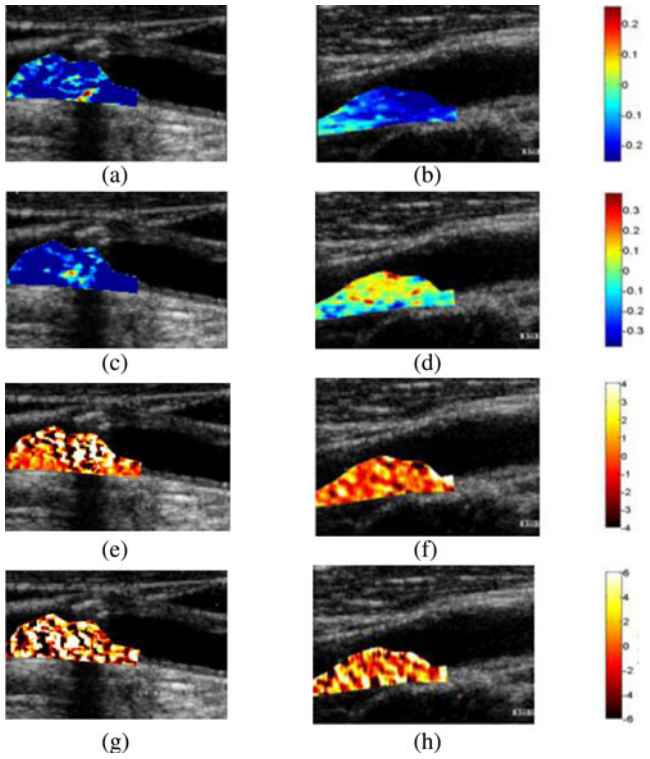

Fig. 2. Color-coded distributions of diastolic (a, b, e, f) radial and (c, d, g, h) longitudinal (a–d) displacements (in mm) and (e–h) strains (%) for (a, c, e, g) an asymptomatic and (b, d, f, h) a symptomatic atherosclerotic patient (colored areas: plaque; dark areas: vessel lumen; and gray areas: tissue surrounding the arteries).

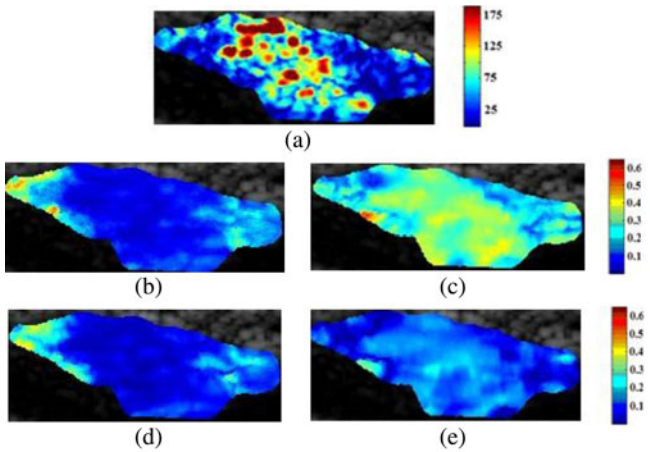

Fig. 3. Color-coded distributions of (a) normalized gray-scale ([0: black, 255: white]) image intensities at diastole for a symptomatic patient. (b–e) show (b, d) radial and (c, e) longitudinal (b, c) velocities (in mm/s) and (d, e) motion amplitudes (in mm) for the same patient. [colored areas: plaque, dark areas: vessel lumen, gray areas: tissue surrounding the arteries].

C. Automatic Segmentation

Segmentation of B-mode ultrasound images of the carotid artery wall deals with delineating the boundaries of different structures, as a step toward clinically useful morphology measurements. Valid identification of the different arterial wall layers in longitudinal views of the carotid artery enables accurate measurements of the thickness of the intima-media complex (IMT). IMT has a significant prognostic and diagnostic role for CA, given that (a) it is a well-known early indicator of the development of cardiovascular disease, (b) it is a validated marker of the progression/regression of atherosclerosis and (c) it can be used to evaluate drug therapy response [44]. Additionally, tracing the near and far wall-lumen interfaces in either longitudinal or transverse sections of the artery allows for diameter measurements and localization of stenoses due to CA [45]. By segmenting a sequence of ultrasound images, it is also possible

to estimate IMT and diameter in different phases of the cardiac cycle [45], [46].

Segmentation is also the key for measurements in the region of the plaque. Total plaque area (TPA) and total plaque volume (TPV) quantify plaque burden in two (2-D) [46] and three dimensions (3-D) [47], respectively. The 3-D vessel wall volume (VWV) measures the vessel wall thickness plus plaque within the carotid arteries and it has been piloted in small clinical trials to calculate carotid burden after drug [21] and dietary interventions [48]. Carotid plaque surface irregularities assessed by ultrasonography have also been shown to independently predict ischemic stroke [49].

Segmentation of the carotid artery wall and plaque in ultrasound images is a prerequisite for automatic, i.e. user-independent, UIA. Such task is a significant challenge, because ultrasound images have an overall quality that is dependent on the scanner settings and the operator expertise. In carotid ultrasound images, another complication is given by the high variability in normal vessel morphology and in vessel appearance under pathology. Robust segmentation methodologies must maintain their efficacy under different ultrasound scanners, scanner settings and operators, morphology (healthy and atherosclerotic arteries), image orientation (horizontal and inclined vessels), and appearance (straight and curved vessels). The algorithms should also be fully automatic to avoid errors due to user interaction for the selection of ROI or/and the initialization step.

Several segmentation methodologies have been developed so far to identify the carotid artery wall from 2-D/3-D B-mode ultrasound images/image sequences. Briefly, these studies used advanced image processing tools, such as active contours [50], edge detection [51], dynamic programming [52], Hough transform [45], and geometrical and modeling methods [53]. Recent studies have used genetic programming [54] and methodologies incorporating anatomical information [55] to achieve more accurate segmentation. Segmenting the region of the plaque remains a particularly challenging task, with less work having been performed in the field [46], [47], [50].

IV. Perspective for a Clinical Scenario for Management of Carotid Atherosclerosis

The ultimate outcome of research on carotid UIA will hopefully be the establishment of a new clinical scenario for optimal and personalized management of CA [see Fig. 1(b)]. In the context of this scenario, treatment selection will be assisted by smart tools which automatically classify an atherosclerotic case. Such tools will 1) identify the plaque presence and boundaries of ROIs; 2) extract UIA-based features (echogenicity/texture, motion/strain, morphology); and finally 3) combine "traditional" criteria (degree of stenosis, symptom status) and the extracted features in sophisticated classification techniques to provide recommendations about plaque vulnerability and appropriate treatment.

During the last decade, considerable attempts have been made in designing classifiers toward this direction. Multiple classification tools, such as support vector machines [13], [19], [20], [56], [57], neural networks [58], probabilistic neural networks [20], [57], self-organizing maps [18], and fuzzy c-means [59], have been used. Most studies have considered echogenicity/texture features [13], [18]–[20], [56], [58], [59] and morphology [13], [18], [57] while motion properties have been investigated in limited cases [59]. Although these attempts have reached 73.1% [18]–99.1% [58] classification, longitudinal studies using large patient samples are still required for valid results. Table I overviews significant cross-sectional and longitudinal studies in this field.

TABLE I
Key Studies on Ultrasound Image Analysis Toward Identifying Risk Markers for Carotid Atherosclerosis

study, design	dataset (# of CA patients)	follow up	suggested risk markers	classification accuracy
[13], A	a) 346 (AS: 150, S:196) b) 71 (AS: 60, S: 11)	-	T, MO	a) 83% b) 89.5%
[18], A	230 (AS: 115, S: 115) *	-	E, T, MO	73.1%
[19], A	20 (AS: 9, S:11)	-	T	85%
[20], A	20 (AS: 9, S:11)	-	T	79.3%
[21], C	435	12 yrs	E, T, MO	-
[22], C	133	2 yrs	E	-
[36], B	45 (AS: 23, S: 22)	-	M	-
[49], C	1092	6.2 yrs	MO	-
[56], A	346 (AS: 150, S: 196)	-	T	83.7%
[57], A	274 (AS: 137, S:137)	-	MO	73.7%
[58], A	108 (AS: 54, S: 54) *	-	E, T	99.1%
[59], A	19 (AS: 9, S:10)	-	E, T, M	84%

*Indicates cases where the # of CA patients was not available, and the # of images is noted, instead.
A, B: cross-sectional study using classifiers and statistical tests, respectively, to discriminate asymptomatic (AS) and symptomatic (S) plaques, C: longitudinal study using statistical tests. CA: carotid atherosclerosis, yrs: years, E: echogenicity, T: texture, M: motion, MO: morphology.

Additionally, within the described scenario, the collected data will be optimally organized by means of semantic technologies. This will allow clinicians to annotate images with formality and efficiently retrieve data through complex search queries [60]. These functionalities will facilitate knowledge discovery and sharing, as well as easy comparisons with similar prior cases for improved patient care.

Besides the refinement of the currently inadequate clinical practice for the disease, the potential offered by this scenario would allow more objective and user-independent diagnostic decisions, because automatic procedures would be followed. Automatic procedures would also help less well-experienced clinicians to effectively evaluate atherosclerotic lesions.

V. Toward Early and Valid Stroke Prediction

According to what has been described previously, it becomes obvious that a number of advanced image processing methodologies have been developed to measure particularly interesting physiological phenomena from ultrasound images. Although the usefulness and applicability of such methodologies has been shown in a number of studies, a systematic application to sufficiently large patient samples so as to address specific clinical challenges has been rather limited. Low clinician demand for clinical decision support is also an important barrier, which is related to usability issues, concerns about autonomy, and legal

and ethical ramifications of adhering to or overriding computer-aided recommendations.

The available UIA methods, and the corresponding features, allow the investigation of many complex phenomena that could not be studied until now. As an example, the regional nature of these methods allows the in-depth investigation of segments of the arterial wall, namely different wall layers, different plaque areas as well as any other wall area indicated by the physician. It should also be stressed that the UIA, and in particular motion analysis and the derived elasticity indices, is able to provide valuable functional, rather than mere anatomical, information, which may be more sensible to early wall changes due to the presence of disease. In this same line of investigation, the use of the previously described features is expected to highlight the effect of various interventions, including dietary and medical ones, on the arterial wall.

Such investigations will produce new knowledge about the complex phenomena of arterial physiology and pathophysiology and will allow the identification of candidate markers for stroke prediction. In this context, animal models offer a particularly important alternative, given that such models are more robust, with lower variability, than human subjects [39]. The actual predictive value of the candidate markers will be confirmed through appropriately designed longitudinal studies, including frequent follow-up procedures. Associations with histological samples will confirm the value of the desired markers.

The last step in the search for novel markers for stroke prediction includes their integration into routine clinical practice. This step includes the design of computer-aided-decision systems based on smart classifiers and the subsequent translation of scientific discoveries into real-world applications, i.e., from laboratory experiments to actual point-of-care patient applications through clinical trials. The previously described steps will lead to the re-definition of the clinical algorithm for the management of CA.

VI. Conclusion

Stroke carries an enormous socioeconomic burden, and its prevention continues to remain one of the major challenges facing the scientific community, despite numerous efforts to highlight the natural history of its underlying cause, namely CA. UIA, in combination with smart tools, has the potential to identify valid, low-cost and noninvasive markers for risk stratification, paving the way for a patient-centered science-driven diagnostic procedure.

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