Computer aided diagnosis of coronary artery disease, myocardial infarction and carotid atherosclerosis using ultrasound images: a review

FAUST, Oliver <http://orcid.org/0000-0002-0352-6716>, ACHARYA, U Rajendra, SAN, Tun Ru, YEONG, Chai Hong, MOLINARI, Filippo and NG, Kwan Hoong

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Computer aided diagnosis of coronary artery disease, myocardial infarction and carotid atherosclerosis using ultrasound images: A review

Oliver Faust[a], U Rajendra Acharya[b,c,d], Vidya K Sudarshan[b], Tan Ru San[b], Chai Hong Yeong[f], Filippo Molinari[e], Kwan Hoong Ng[d,*]

[a]*Department of Engineering and Mathematics, Sheffield Hallam University, United Kingdom*
[b]*Department of Electronic & Computer Engineering, Ngee Ann Polytechnic, Singapore*
[c]*Department of Biomedical Engineering, School of Science and Technology, SIM University, Singapore*
[d]*Department of Biomedical Engineering, Faculty of Engineering, University of Malaya, Kuala Lumpur, Malaysia*
[e]*Department of Electronics and Telecommunications, Politecnico di Torino, Turin, Italy*
[f]*Department of Biomedical Imaging, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*

Abstract

The diagnosis of Coronary Artery Disease (CAD), Myocardial Infarction (MI) and carotid atherosclerosis is of paramount importance, as these cardiovascular diseases may cause medical complications and large number of death. Ultrasound (US) is a widely used imaging modality, as it captures moving images and image features correlate well with results obtained from other imaging methods. Furthermore, US does not use ionizing radiation and it is economical when compared to other imaging modalities. However, reading US images takes time and the relationship between image and tissue composition is complex. Therefore, the diagnostic accuracy depends on both time taken to read the images and experience of the screening practitioner. Computer support tools can reduce the inter-operator variability with lower subject specific expertise, when appropriate processing methods are used. In the current review, we analysed automatic detection methods for the diagnosis of CAD, MI and carotid atherosclerosis based on thoracic and Intravascular Ultrasound (IVUS).

*Corresponding author

We found that IVUS is more often used than thoracic US for CAD. But for MI and carotid atherosclerosis IVUS is still in the experimental stage. Furthermore, thoracic US is more often used than IVUS for computer aided diagnosis systems.
Keywords: Computer Aided Diagnosis, Coronary Artery Disease, Myocardial Infarction, Carotid Atherosclerosis, Thoracic Ultrasound, Intravascular Ultrasound

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1. Introduction

Cardiovascular disease has been a global public health problem for the last 35 years [1]. Public health statistics show that the number of patients, with some form of cardiovascular disease increase steadily in countries with a low and middle gross national income, while a number of countries with a high gross national income have managed to diminish the incidence of cardiovascular disease [2, 3]. On a global scale, cardiovascular disease is responsible for around 30% of human mortality as well as 10% of the disease burden [4, 5]. In 2005, 17 million out of 58 million deaths worldwide were caused by cardiovascular disease [6, 7, 8, 9]. According to the statistics, published in 2013, the various risk factors causing death are 40.6% due to high blood pressure, 13.7% came from smoking, 13.2% resulted from a poorly balanced diet, 11.9% are attributed to insufficient physical exercise and 20.6% could not be attributed [10, 11]. Another noteworthy result was the fact that 88% of all cardiovascular fatalities had abnormal glucose levels [12, 13]. Coronary Artery Disease (CAD) is a specific cardiovascular disease, which affects the coronary arteries of human heart. Having CAD carries the risk that the patient may develop Myocardial Infarction (MI) [14]. The pathology of MI is characterised by an occlusion in a coronary artery which leads to the death of myocardium [15]. Each year in the United Kingdom, there are more than 250,000 documented acute MIs, with at least the same number of patients being admitted to hospital to rule out acute MI. The diagnosis of acute MI is difficult, because of time pressure and complexities of medical data interpretation. Traditionally, the diagnosis is based on a combination of clinical history, Electrocardiography (ECG) findings and biochemical tests [16]. To prevent or at least reduce the number of MI events it is necessary to monitor the cardiac health of a patient. Studies show that carotid plaque is a good predictor of cardiovascular diseases [17, 18]. Thoracic Ultrasound (US) is widely used to diagnose carotid atherosclerosis [19, 20, 21]. In recent years, computer support systems have moved on from mere plaque detection to plaque characterization. Despite considering multiple data sources and improved image analysis methods, the diagnosis of CAD, MI and carotid atherosclerosis still lacks Sensitivity (Se) and Specificity (Sp).

US images can provide vital information for the diagnosis of CAD, MI and carotid atherosclerosis. However, they are often distorted and incomplete which makes them open to multiple interpretations [22]. Therefore, the diagnostic relevance of a randomly selected US image falls within a wide range. For a significant number of images the diagnostic relevance is below a threshold where relevant features are ambiguous, and hence the practitioner has to depend on experience to establish reasonable inference [23, 24]. A US scan is a gradual process; hence the image interpretation is revised as soon as new information is revealed [25]. Consequently, there are distinct hierarchical levels of interpretation [26]. A reading radiologist must have expert knowledge in the language used to describe the images as well as an excellent understanding of the relationship between pixel grey levels and the anatomical objects, to ensure that all interpretations are uniform and are of high quality [27]. Apart from the inherent difficulty to extract diagnostic information from US images, there is also the problem of data overloading [28]. Progress in US imaging means to produce more data during scanning [29, 30]. A human screener might spend a significant amount of time to get the required information. For computer aided diagnosis, data overloading is not a problem, as digital processing and data storage will take care of this [31]. Consequently, computer support systems handle the increasing data volumes much better than human practitioners. Hence, the question shifts from whether there is computer support, for US based cardiovascular disease diagnosis, to how reliable is the computer support. The most advanced computer support systems incorporate machine learning and artificial decision making algorithms [32, 33]. Potential application areas for computer aided diagnosis systems are treatment monitoring [34], drug efficacy tests [35] and most importantly disease detection [36].

A well-designed computer support system can reduce the cost and improve the quality of US based diagnosis. Replacing human work with computer processing yields these benefits. Computer support systems can be mass produced; hence manufacturers can improve their sales and thrive in a competitive market. Using computing technology keeps the systems flexible and it is easy to incorporate the latest progress in the relevant fields of medicine, computing and engineering through hardware and software upgrades. In this review, of US based diagnosis of CAD, MI and carotid atherosclerosis, we highlight that these diseases are linked and hence the processing techniques, used for diagnostic support, should be similar as well. We found, that the processing techniques depend on whether thoracic US or Intravascular Ultrasound (IVUS) is used for image acquisition. During our review, we learned that IVUS is predominantly used for CAD diagnosis, whereas thoracic US is mainly used for MI. For the diagnosis of carotid atherosclerosis, the invasive nature of IVUS is a problem. Therefore, the intravascular method is still experimental, hence it is mostly used for post mortem studies. We are surprised to find only one computer aided diagnosis system based on IVUS. We suspect that the lack of IVUS based computer aided diagnosis systems comes from the fact that the imaging modality is relatively new, hence the research focuses on image analysis rather than diagnosis support. We adopt the position that there is a need for IVUS based computer aided CAD and MI diagnosis. Creating such IVUS based diagnosis support tools is a logical progression from focused imaging modalities. These systems are very relevant, because they can improve the efficiency of practitioners by reducing the amount of time spent in scanning the US images. In the long run, computer aided diagnosis systems reduce the cost and increase the diagnostic accuracy.

The article is organized as follows. The next section provides the necessary background on CAD, MI and carotid atherosclerosis. Section 3 introduces the materials and methods used to design computer support systems for US based cardiovascular disease diagnosis. The results section lists diagnostic support systems for CAD, MI and carotid atherosclerosis. We focus on discriminating Artificial Intelligence (AI) based computer aided diagnosis systems from non AI based computer support systems. Practical settings and limitations are covered in the discussion section. Section 6 concludes the review.

2. Background

2.1. Coronary Artery Disease

Coronary arteries provide oxygen and nutrients to heart muscles. They are composed of three basic layers: the intima, media, and adventitia which are arranged into three concentric layers. Any disease that affects the coronary arteries causes systemic disability and in some cases death. The major cause of CAD is atherosclerosis, which is characterized by the deposition of cholesterol and lipids, predominantly within the intimal wall of the artery [37]. CAD is a progressive condition that takes several years to develop [38]. The phases of atherosclerosis progression are fatty streak, fibrous plaque, and complicated lesion. The initial fatty streaks are marked by lipid-filled smooth muscle cells [37]. Later, a yellow shade appears when fatty streaks progress within the smooth muscle cells. The subsequent fibrous plaque phase exhibits the onset of continuous ongoing alterations in the endothelium of the arterial wall. The fatty streak is eventually covered by collagen forming a fibrous plaque that appears greyish or whitish [39]. These plaques can develop on one section of the artery or in a circular manner, comprising the entire lumen. The last phase, in the progression of the atherosclerotic lesion, is the most threatening. The continuous growth of plaque, which causes inflammation, results in plaque instability and rupture [39]. Later, platelets gather in large numbers, resulting in the formation of a thrombus. The thrombus sticks to the arterial wall, causing to additional narrowing or complete occlusion of the artery. During the early stages, a patient experiences little or no symptoms, but if the causes of CAD remain, the disease progresses. Hence, treatment will start with eliminating the causes and in more serious cases medication will be administered. Without intervention, a CAD patient can develop ischemia (intermittent blood supply) and then infarctions (loss of blood supply). These serious conditions can lead to Sudden Cardiac Death (SCD) [40].

Forbes at al. found a statistically relevant correlation between plaque in the coronary arteries and a greater long term risk of contracting CAD [41]. With current IVUS technology it is possible to differentiate four different plague types: necrotic core; dense calcium; fibro-fatty; and brous [42, 43]. Coronary artery plaques with a thin fibrous cap over a large necrotic core are more prone to rupture [44, 45]. In a focused review, Banach et al. analysed the efficiency of statin therapy on fibrous plaque[46, 47]. 830 subjects participated in the reviewed clinical studies, 737 were given statin and 93 were in the placebo control group [48, 49, 50]. Their analysis shows that statin therapy reduces fibrous plaque, but the necrotic core volume remains unchanged [51, 52]. Nozue et al. used virtual histology IVUS in a clinical study about the effect of fluvastatin on coronary plaque [53]. It is found that, apart from evaluating the plaque morphology, the mechanical properties of the coronary arteries are also important in evaluating the CAD [54, 55]. Establishing the mechanical strain pattern of the artery wall can help to determine whether a lesion is unstable and prone to rupture. Changes in the coronary artery blood flow can be interpreted as signs of CAD [56]. Therefore, features based on fluid dynamic algorithms carry diagnostically important information which can be used in future computer aided diagnosis systems.

Contrast angiography is the gold standard for diagnosing the extent of CAD [57, 58]. But, its limitation is that visually analysed angiography results in underestimating atherosclerosis in "normal" coronary artery segments [59, 60]. Govindaraju et al. reviewed the functional severity of coronary artery disease with fluid dynamics [61]. They found that fractional flow reserve is a standard index to identify the severity of CAD. It can be used to avoid surgical complications by estimating pressure drop and flow reduction caused by invasive interventions. Flow models were also used to estimate artery wall stress, which appears to contribute significantly to CAD [62]. US is frequently used to assess the coronary arteries. Figure 3 shows thoracic images of the human heart, which can be used to assess the coronary arteries. Figure 4 shows IVUS images from within a coronary artery. The three-layers of the coronary artery appear as the bright inner layer (intima), middle echo-lucent zone (media), and outer bright layer (adventitia) in a cross-sectional view using IVUS. Detecting these layers of vessel provides orientation in the IVUS image. Assessing the coronary artery is important, because CAD can progress towards more dangerous cardiovascular diseases, such as MI. The next section explores the relationship between CAD and MI.

2.2. Myocardial Infarction

MI manifests in a wide range of symptoms. The spectrum reaches from an absence of symptoms over a minor event to a major event, which can result in SCD or severe haemodynamic deterioration [63]. MI results from a progressive collection of atherosclerotic plaque on the walls of coronary arteries [64]. The accumulated plaque gets ruptured initiating a clot which results in complete blockage of the artery. Angiography is performed to detect narrowing or complete blockage of the infarct-related coronary artery [65, 66]. The artery occlusion decreases the blood flow to the myocardium, which damages the heart muscle [67]. If reduced blood supply to the myocardium persists long enough, a process called ischemic cascade is initiated [68] whereby the heart cells begin to die, causing a condition called MI. Accordingly, the patient's heart will be permanently (irreversibly) damaged [69].

For many cases, CAD progression occurs in previously insignificant lesions [70]. It is very often observed that lesions of acute MI have severe stenosis. Even though the stenosis is severe, it is second to the superimposed thrombus. However, before the event, severe stenosis might not occur [71]. Acute MI is caused by one of two events. The first event is a sudden rupture or ulcer in a coronary artery [72]. The second cause is the formation of vulnerable plaque which leads to a thrombus blocking the coronary artery. The speed with which the catastrophic event unfolds leaves little or no time for counter measures. Vulnerable plaques can be characterized by a fibrous cap with macrophage infiltration and a large lipid pool [73]. Cardiologists examine different cross-sectional planes with various US transducer positions to assess left ventricular wall segments. They use the same technique to view and detect MI [74]. Figure 3b shows a thoracic USimage of an MI affected heart. Plaque and plaque formation analysis is also of paramount importance for diagnosing carotid atherosclerosis.

2.3. Carotid Atherosclerosis

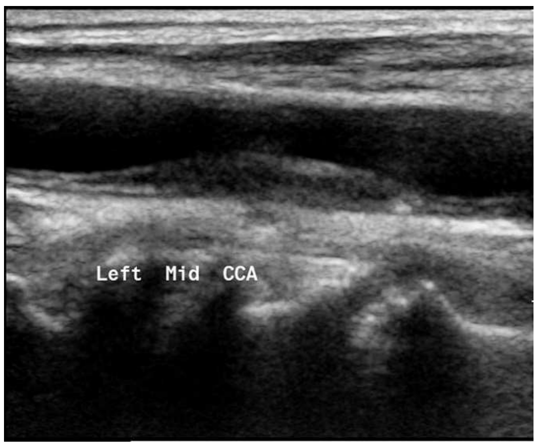
The carotid arteries are the two large blood vessels (internal and external carotid arteries) that supply oxygenated blood to the large, front part of the brain [75]. Like coronary arteries, carotid arteries are also susceptible to atherosclerosis, an inflammatory accumulation of plaques. These plaques contain Lipid-Rich Necrotic Core (LRNC), which is enclosed by depleted smooth muscle cells and a thin fibrous cap [76]. Thinning of these fibrous cap is a distinct risk indicator for underlying or forthcoming ischemic neurological abnormalities [77, 78]. Emboli or thrombus may break off, due to artery wall stress, from plaque having a thin fibrous cap and join the blood circulation towards the brain [79]. As the vessel becomes narrower, the thrombus gets attached to the vessel wall and cause carotid artery stenosis [80]. The formation of carotid artery stenosis either diminishes or restricts blood flow to brain regions which are supplied by the vessel, thereby causes Transient Ischemic Attacks (TIAs). TIAs are warning signs, frequently followed by severe permanent (irreversible) thromboembolic stroke [81, 82, 83]. Further extension of this condition may lead to loss of brain function or even death.

Carotid stenosis, due to atherosclerosis, is grouped into asymptomatic [84] and symptomatic [85]. Asymptomatic carotid stenosis denotes around 60% narrowing of proximal carotid artery in the absence of earlier history of stroke or TIA [86]. Symptomatic carotid stenosis is frequently linked with type 5 (having more extracellular lipids, hematoma) or 6 (having surface defect, hematoma and thrombosis) plaques [76]. The presence of larger LRNC, in both symptomatic and asymptomatic carotid stenosis a thin or ruptured fibrous cap [87]. Thus, the accurate identification or classification of symptomatic and asymptomatic carotid stenosis is important for selecting appropriate treatment [88]. The ability of a particular treatment to prevent stroke, in both symptomatic and asymptomatic patients having chronic carotid stenosis, is the topic of ongoing research [89, 90, 91]. Figure 1a shows a US scan of the dangerous systematic plaque. Figure 1b shows a section of the carotid artery with asymptomatic plaque. In contrast, Figure 1c shows a US image of a normal carotid region.

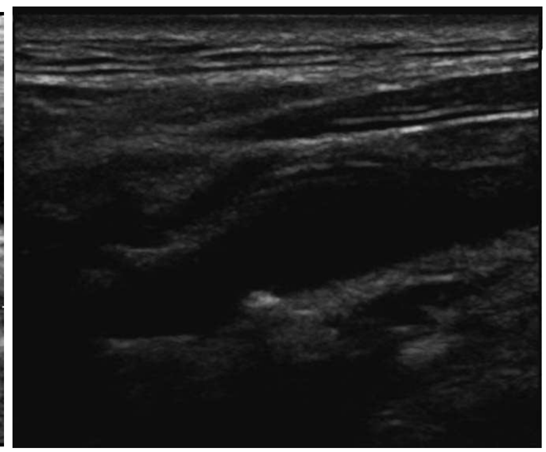
The minimal invasive method of contrast enhanced Curvelet Transform (CT) has been used to quantify carotid plaque [92]. These systems are used for carotid plaque segmentation. US is a preliminary non-invasive imaging technique that can be used to assess carotid artery stenosis [93]. In clinical settings, high-resolution, B-mode US together with Doppler flow is often used for assessing carotid arteries [94]. Furthermore, Doppler US is also used for the characterization of high risk plaques and thus help in for assessing the severity of stenosis [95]. A main restriction of this imaging modality is that it is highly user dependent. Therefore, advancements in non-invasive imaging technology, using computer-aided methods, have enhanced the acquisition of data and significantly improved the diagnostic accuracy. In the next section, we explore the design of US based diagnosis systems for cardiovascular diseases.

3. Diagnosis support system design

On a conceptual level, we discuss two different design strategies for CAD, MI and carotid atherosclerosis diagnosis support systems. The first system design approach yields implementations, which provide just analytical support. This support can range from simple US image enhancements to 3D reconstruction of coronary arteries [96]. In general, these systems extract relevant information which helps cardiologists with their diagnosis [97, 98]. Computer aided diagno-



(a) Symptomatic plaque.



(b) Asymptomatic plaque.

(c) Normal

Figure 1: Thoracic US images of carotid arteries.

sis systems aim to provide efficient diagnosis. Hence, these systems can be used to automate the diagnosis process, which has important benefits including but not limited to a large cost saving potential. Therefore, computer aided diagnosis became the focus of major research work in medical imaging. Furthermore, these systems are of interest in diagnostic radiology [99]. All diagnostic support systems assist practitioners by extracting features from underlying data [100]. The underlying data comes from physiological measurements or medical images [101]. A computer aided diagnosis system uses these features as input to decision making processes. The system communicates the decision results in the form of a diagnosis to the practitioner. Computer aided diagnosis systems with low complexity or systems which must deal with particularly difficult data, offer only disease or non-disease diagnosis. In contrast, more sophisticated systems, which might be based on the combination of different imaging modalities and physiological measurements, may have to diagnose number of classes (stages of diseases). Regardless of the system complexity, the classification performance determines the computer aided diagnosis quality. Hence, the classification performance is used to select and compare the systems [102]. To achieve a high classification performance, it is necessary to carry out statistical performance tests of features during the training phase.

In the sections below, we adopt the design perspective to explain diagnostic support systems used for CAD, MI and carotid atherosclerosis based on US images. On the highest level of abstraction, the design is partitioned into an online and an offline system. Such a conceptual split is very important, because the offline system allows the designer to focus on creating, benchmarking and selecting the most appropriate algorithm structure. In contrast, an online system uses the selected algorithm structure to provide diagnosis support. The left part of Figure 2 shows both algorithm structure and statistical tests carried out in the offline system. The online system deals with unknown US images. The offline system uses known or labelled US images as input. The input images are subjected to pre-processing and feature extraction. In the offline system, a range of methods are tested and only the most efficient algorithms are used in

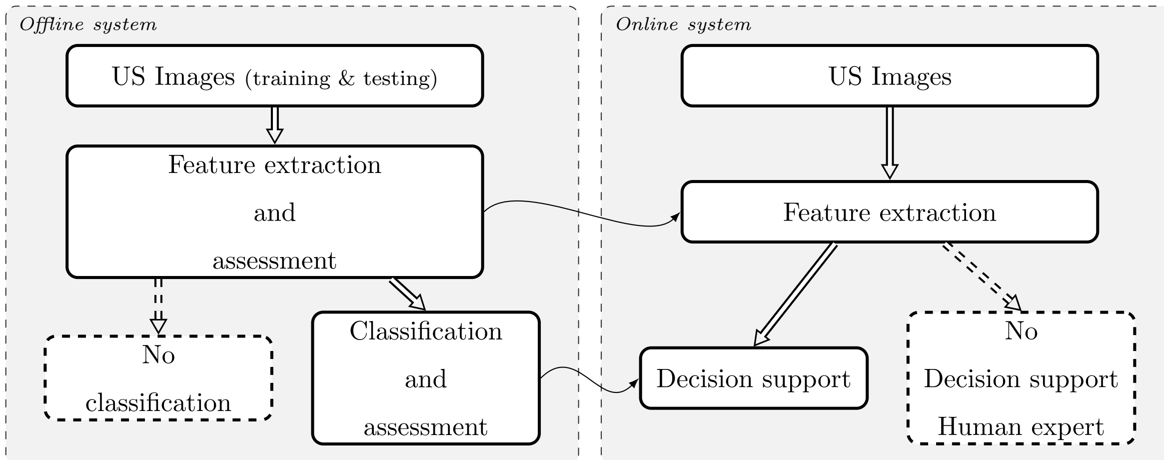


Figure 2: A block diagram depicting the highest level of abstraction for the design of a computer support systems for CAD, MI and carotid atherosclerosis based on US images. The diagram highlights the fact that, unlike normal support systems, computer aided diagnosis systems provide decision support through automated classification.

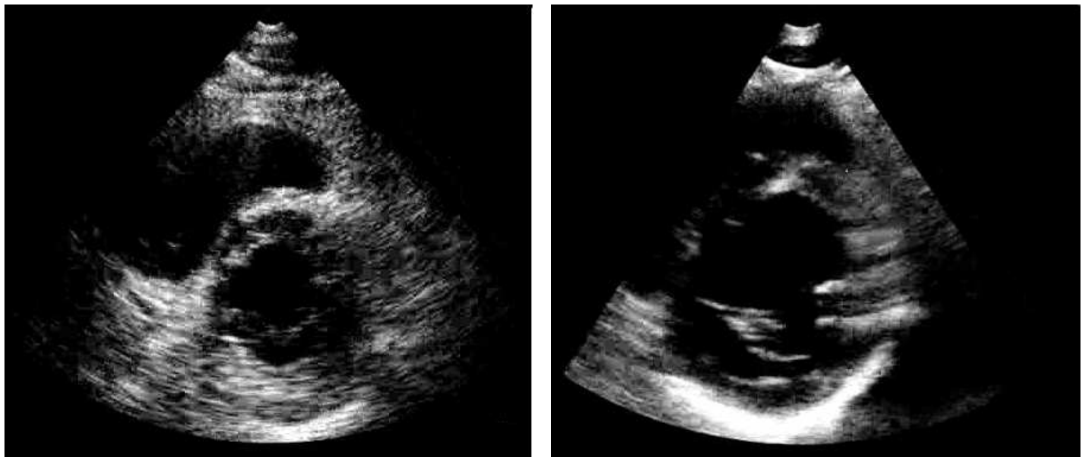
the online system. Similarly, the designer tests several classification algorithms in the offline system and the online system uses only the best decision making method. Simple computer support systems do not have a classification step, only computer aided diagnosis systems include such algorithms. In general, testing more algorithms creates more competition which improves the system performance. The feature extraction algorithms take images from thoracic US or IVUS. These image acquisition methods are discussed below.

3.1. Ultrasound Image Acquisition

Thoracic echocardiographic technology has the advantages of portability, mature technology and low image acquisition cost [103]. Furthermore, the cardiovascular system assessment results, for both doppler and 2D thoracic US imaging modalities, have been validated with other diagnostic imaging techniques, such as CT [104]. Echocardiography is most commonly used to assess the cardiac chamber and establish the extent of its functionality. Especially for analysing the cardiac chamber functionality, the realtime nature of echocardiography is beneficial, because moving images report chronological as well as spatial information. Standardization of the methodology, used to assess cardiac chambers, is established by collecting, creating and disseminating scientific research results, which, when followed by practitioners, provide uniformity and facilitate unambiguous communication [105].

Despite the efforts of standardisation, US imaging poses a number of challenges for image analysis and feature extraction [26]. First and foremost, the relation between pixel intensity and tissue properties is complex, because of the acoustic phenomena used for image acquisition. US systems send high frequency sound waves (typically 1 MHz to 18 MHz) through human tissue and record reflected, as well as scattered, signal components. The US system displays these received signals on a screen. Tissue transitions are represented by reflections. Wave scattering results in interference pattern, known as speckle pattern. Hence, US images are an overlay of speckle pattern and sharper reflection structures. In many cases, different tissues can only be distinguished based on minute changes in the speckle pattern. These changes might even be transient, which makes it necessary to observe a sequence of US images over a period of time. Furthermore, US images depend on operator specific properties, like angle and depth of the US beam [106]. In addition, the images might include artefacts and image noise [107]. Another big problem is missing information, such as dropouts, shadowing, scan sector limitations and restricted echo windows [108]. Fast moving structures can also cause aliasing effects which result in spatial distortion [109]. In general, the relationship between tissue formation and image texture is better defined for medical imaging modalities that use ionizing radiation, such as computed tomography (Hounsfield units) and X-ray (Lambert-Beer law) [110]. It takes an experienced practitioner to overcome the problems of US image interpretation [111]. Computer support systems must incorporate functionality which mimics that creative process.

US image acquisition is a gradual process; therefore, an image represents a snapshot of the information available. Figure 3a shows a typical US image of a normal human heart while Figure 3b shows an MI affected heart. For the



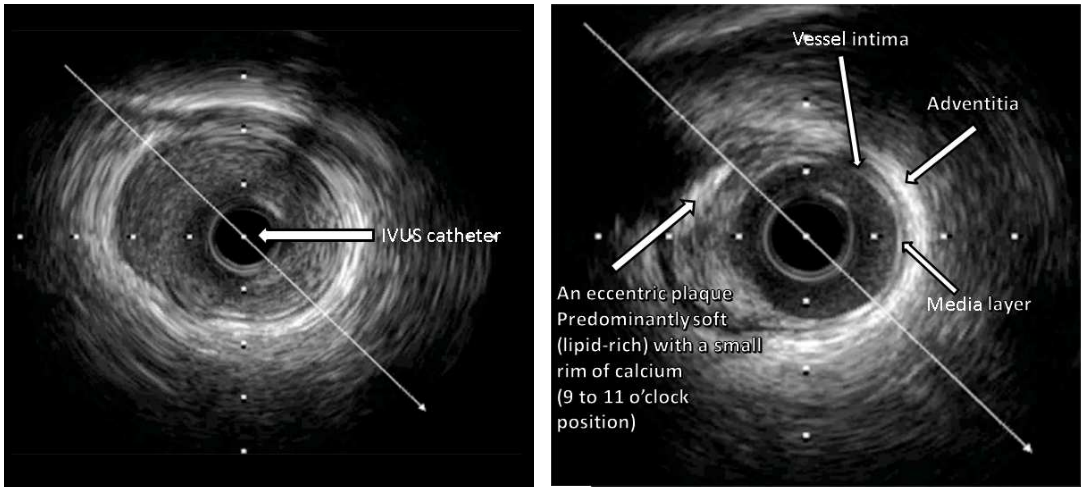
(a) Normal (b) MI affected.

Figure 3: Thoracic US images of human hearts.

untrained eye, the features, which distinguish normal and MI images are not clear. It requires expert training to build up the knowledge to distinguish MI from normal. To establish such an expert knowledge is the challenge for the design centric offline system. The online system must provide the features that give the diagnosis in a practical setting.

3.1.1. Intravascular ultrasound imaging

The first IVUS images of normal and atherosclerotic arterial wall thickness is published by Mallery et al in 1988 [112]. Hence, it is a relatively new medical imaging modality. IVUS delivers precise tomographic images which enable the reading radiographer to assess coronary arteries *in vivo* [113]. Clinical studies established that IVUS is sensitive in detecting atherosclerosis and quantifying both plaque geometry as well as structure. However, the effectiveness for providing diagnostic support is limited due to the two-dimensional signal representation, which is still used in most systems [114]. Analytical computer support systems aim to improve the information presentation by making it more accessible, for example through 3D representation.



(a) Normal. (b) Diseased.

Figure 4: IVUS of coronary artery segments – Left Anterior Descending view.

The physical IVUS set up is established by mounting a US transducer on the tip of a catheter. The catheter is inserted into an artery where the US sensor captures intravascular images. These images depict the morphology of both plaque and arterial wall [115]. IVUS can help to detect the presence and to determine the atherosclerosis composition in angiographically normal reference sites [116]. Computer support systems extract information bearing features from these images. In contrast to thoracic US, IVUS is invasive [117]. The act of inserting the US transducer can, amongst other complications, cause plaque to come loose from the artery wall [118]. Plaque debris in the carotid artery can cause stroke and plaque derbies in the coronary artery can cause MI.

Like thoracic US images, IVUS images are difficult to interpret. Figures 4a and 4b show typical IVUS images of normal and diseased coronary arteries, respectively. Detecting vessel intima, adventitia and media layer provides orientation in the IVUS image. However, the challenge is to detect and characterize plaque. The first step to tackle that challenge is to employ effective feature extraction methods.

3.2. Feature extraction and assessment

Feature extraction is a process which determines one or multiple information bearing properties from an US image to form a feature vector [119]. US image interpretation requires the conversion of image textures into features. The underlying assumption is that image textures contain diagnostically relevant information [120]. The features extract as well as condense the information and present it as a parameter value [121]. Statistical methods, such as Analysis Of Variance (ANOVA) with p- and F-values, can be used to select and rank the features. However, statistical tests assume that the known test data has specific statistical properties. For example, ANOVA assumes a Gaussian distribution. As a consequence, these statistical test methods provide just an indication of what features should be used for classification. The final feature selection is based on classification results. The classification performance depends, to a large extent, on the selected features. Hence, feature extraction and selection are crucial processes in the design of computer aided diagnosis systems. The following list details feature extraction methods used in the reviewed computer support systems:

- Texture features, such as the Gray-Level Co-occurrence Matrix (GLCM) [122], are widely used for MI diagnosis. The strength of texture features lies in extracting information which relates to the spatial entanglement of intensity values within the Region of Interest (ROI) of an US image. A significant weakness of texture features comes from the fact that most texture extraction algorithms depend on both image and grey scale resolution.

- Statistical features, such as Principal Component Analysis (PCA) and Higher Order Spectra (HOS) [123] are found to be effective. The advantage of statistical features is that they are robust in the presence of noise. That robustness depends on the length of data that can be averaged. Being and essentially linear methods, statistical methods fail to capture nonlinear information contained in US images.

- Transform domain features, such as Discrete Wavelet Transform (DWT) [124], Stationary Wavelet Transform (SWT) [125] and CT [126]. As such, CT generalizes wavelet transform results to represent US image structures in terms of scale, orientation and location [127, 128]. Transform domain features detect subtle changes in the US image. The methods perform well in the presence of noise and low computational complexity algorithms exist for standard feature extraction. A disadvantage of these methods is that establishing the transform domain is insufficient, another processing step is needed to extract a specific feature.
- Features based on configuration information, such as Local Configuration Pattern (LCP) combines local structural [129] and microscopic [130] configuration information which can be used for image classification. That hybrid feature extraction method has potential. However, practical computer support systems should use more than two feature extraction methods, to harvest the benefits and at the same time minimize the disadvantages of the individual methods.

3.3. Classification

Only computer aided diagnosis systems incorporate a classification step. The classification is established through artificial learning and decision making algorithms. All, except the study by Thangavel et al. [131], reviewed computer aided diagnosis systems used supervised learning algorithms. Unsupervised differ from supervised learning algorithms in the way the clusters are established [132]. Unsupervised learning algorithms establish clusters in the data [133]. Unknown feature vectors are labelled as belonging to one of these clusters. Supervised learning is based on classical ideas of a student and teacher relationship [134]. In terms of machine learning, that relationship is expressed as extracting algorithm parameter from labelled training data. Once the machine learning algorithm is trained, it is tested with labelled data that is not used during the training phase. The test results are expressed in terms of Accuracy (A), Se and Sp [135].

Only the design centric offline system incorporates an assessment step. The most suitable classification algorithm, for the practical online system, is selected based on the assessment results [135]. The following classification algorithms were used in the reviewed US based CAD, MI and carotid atherosclerosis computer aided diagnosis systems:

- Threshold classification is a simple algorithm which classifies based on whether or not a feature value has crossed a specific threshold [136, 137]. The threshold value is established during the training phase.
- Unsupervised learning, such as Self Organizing Map (SOM) [138]. The clusters are established through weight updates in a local area of the map space.
- Classical supervised machine learning, such as Relevance Vector Machine (RVM) [139], K-Nearest Neighbour (K-NN), Gaussian Mixture Model (GMM), Decision Tree (DT), Naive Bayes Classifier (NBC), Probabilistic Neural Network (PNN) [140], and Support Vector Machine (SVM) [141, 142] are used in decision support systems. For many classification tasks, SVM outperforms other methods due to nonlinear kernel functions.
- Classification problem formulated as an optimization question and solved with Binary Particle Swarm Optimization (BPSO) [143, 144].
- Classification problem formulated as an optimization question and solved with Genetic Algorithm (GA) [145].
- Minimum distance classifier uses an algorithm that compares a feature vector with two or more vectors which represent the individual signal classes. The method is often used in image processing [146].

4. Diagnosis support system realisations

The review of computer support systems for CAD, MI and carotid atherosclerosis based on US images was structured according to the design principles outlined in the previous section. During the review, we established whether Internal (I) or Thoracic (T) US was used for image acquisition. Having that information is important, because the feature extraction methods depend on the image type. For example, a 3D coronary artery wall reconstruction feature [96] makes sense only for IVUS. Next, we determined which classifier was used for diagnostic support. Simple analysis systems lack automated classification, hence these systems offer only analytical results and they depend entirely upon human expertise to reach the diagnosis. The design of all reviewed systems was based upon labelled US images, usually taken from patients and normal subjects. As part of the review, we determined the number of datasets used in each work, which helps to establish the performance results, such as A, Se and Sp.

We present the review results in three tables. Table 1 focuses on 17 computer support systems for CAD diagnosis. The table details the review results in accordance with the assessment rubrics discussed above. The materials section provides background on the specific features and classifiers used in the investigated systems. Table 2 details the review results of computer based MI diagnosis support. The table introduces the review results for 16 diagnosis support systems. The columns of this table convey the same information as Table 1. Table 3 presents the review results for 11 carotid atherosclerosis computer support systems in a similar way. In the discussion section, we compared the review results for the considered cardiovascular diseases.

Table 1: Summary of the review results for CAD diagnosis support systems based on Thoracic (T) ultrasound and Internal (I) ultrasound - in most cases IVUS.

Authors	US Type	Features	Classifiers	No. of subjects	Performance measure
Nissen et al. [147]	I	Lumen Size and Wall Morphology	–	51 (8 N and 43 CAD)	Descriptive comparison
Goar et al. [148]	I	Artery diameter	–	20	IVUS vs. angiography

Mintz et al. [149]	I	Lesion calcification	–	110	First order statistics
Potkin et al. [150]	I	Stenosis diameter	–	51	Description
Hermiller et al. [151]	I	Arterial narrowing	–	38	Visual inspection
Alfonso et al. [152]	I	Plaque area	–	27	Vessel compliance
Mintz et al. [153]	I	Artery cross section	–	884	Angiography vs. IVUS comparison
Mintz et al. [154]	I	Plaque mass	–	209	Angiography vs. IVUS comparison.
Klingensmith et al. [155]	I	Image segmentation	–	Three motorized pullbacks	Description
Cothren et al. [96]	I	3D reconstruction of the coronary artery wall	–	Description	
Schoenhagen et al. [156]	I	Remodelling ratio	–	85	Angiography vs. IVUS comparison.
Schartl et al. [157]	I	Scale value analysis	–	131	Drug efficiency statistics
Çomak et al. [158]	T	DWT; Spectrograms	SVM	215 (95 N, 120 CAD)	Se=94.5%, Sp=90.0%, five fold cross validation
Babaoğlu et al. [159]	T	PCA	SVM	480	A=76.67%

Shalbaf et al. [136]	T	Nonrigid image registration	Threshold	14	72% to 92%
Mukhopadhyay et al. [160]	T	Epicardial and Endocardial Border Detection	–	44	–
Araki et al. [32]	I	Grayscale features	SVM	15	A=94.95%

Table 2: Summary of the review results for MI diagnosis support systems.

Authors	US Type	Features	Classifiers	No. of subjects	Performance measure
Skorton et al. [161]	T	Grey level distribution, kurtosis, skewness	Manual classification	7 adult dogs	Se=90%, Sp=70%
Kamath et al. [162]	T	Pixel intensity	Statistical classification	15	Not mentioned
Tak et al. [163]	T	Pixel intensity	Statistical classification	17 (5 N, 12 MI)	Date based MPI statistics
Mojsilovic et al. [164]	T	DWT energy	Unsupervised classification	15	A=96%
Nesković et al. [165]	T	DWT energy	Distance classifier	18	On day 2: Se=73%, Sp=86%, A=78%; Week 1: Se=91%, Sp=86%, A=89%; Week 3: Se=100%, Sp=100%, A=100%
Kotani et al. [166]	I	Lesion as well as proximal and distal reference	–	78	Culprit plaques statistics
Ehara et al. [167]	I	Artery dimension	–	178	Frequency of calcium deposits
Hong et al. [168]	I	Computerized planimetry	–	235	Plaque rupture frequency

Skorton et al. [169]	T	Grey level distribution, kurtosis, skewness	RVM	173	A=84.17%
Moldovanu et al. [170]	T	Mean grey level, skewness, kurtosis and entropy	–	12 (6 N 6 MI)	Entropy: 6.23 ± 0.52 vs. 9.95 ± 0.17
Agani et al. [171]	T	GLCM and DWT	Distance classifier	17	A=91.32%
Acharya et al. [172]	T	BPSO and GA	SVM	15	A=81.46%, three fold cross validation
Sudarshan et al. [173]	T	DWT	SVM	160 (80 N, 80 MI)	A=99.5%, Se=99.75%, Sp=99.25%, ten fold cross validation
Sudarshan et al. [33]	T	Texton features	PNN	160 (80 N, 80 MI)	A=94.37%, Se=91.25%, Sp=97.50%
Sudarshan et al. [174]	T	CT, LCP	SVM	120 (40 N, 80 MI)	A=98.99%, Se=98.48%, Sp=100%
Sudarshan et al. [175]	T	SWT and relative wavelet energy and entropy	SVM	160 (80 N, 80 MI)	A=96.20%, Se=97.5%, Sp=95.0%

Table 3: Summary of the review results for carotid atherosclerosis diagnosis support systems.

Authors	US Type	Features	Classifiers	No. of subjects	Performance measure
Tsiaparas et al. [176]	T	DWT, Discrete curvelet transform, Finite ridgelet transform	SVM	20 atheromatous plaques	Discrete curvelet transform: A=84.9%
Thangavel et al. [131]	T	SOM ADAboost	Contourlet transform	257 carotid US images	SVM: A= 85.6%
Christodoulou et al. [177]	T	Texture, Chaos, Spectrum, Shape	SOM, K-NN	230 US images	SOM:A=73.1%

Acharya et al. [178]	T	Texture	SVM	99	SVM with Radial Basis Function (RBF): A=91.7%, Se=97% and Sp=80%.
Acharya et al. [179]	T	Texture	SVM, DT, GMM, K-NN, NBC, PNN, Sugeno Fuzzy	346 carotid plaque ultrasound image	A 89.5%.
Acharya et al. [180]	T	Texture, DWT, HOS	SVM	146 carotid bifurcation plaques in 99 patients	A=91.7%, Se=97%, Sp=80%
Acharya et al. [181]	T	Texture, Trace transform, HOS, Spectrum	SVM	160 plaques	A=90.66%, Se=83.33%, Sp=95.39%
Acharya et al. [182]	T	Texture, DWT	SVM, GMM, PNN, DT, K-NN, NBC		SVM: A=88%, Se=90.2%, Sp=86.5%
Nair et al. [183]	I	Spectrum	DT	51 post-mortem	A=79.7% for fibrous, A=81.2% for fibrolipidic, A=92.8% for calcified, and A=85.5% for calcified-necrotic regions
Prati et al. [137]	I	Plaque measurements	Threshold	2 carotid arteries post-mortem	Se=65%, Sp=95%
Irshad et al. [184]	I	Visual inspection	–	5 Cases	–

5. Discussion

It is evident from this review that several computer-aided methods are developed using texture features in order to investigate the health of myocardium [174, 33, 175] and carotid artery [180, 178, 182, 179]. Acharya et al., [180] applied DWT, HOS and texture methods to analyse the US images of carotid artery to characterize symptomatic and asymptomatic carotid atherosclerosis. Studies by Sudarshan et al., used second-order spatial statistical analysis together with wavelet, HOS, DWT [173], SWT [175], textons [33], Local Binary Pattern (LBP) [174], and LCP [174] to extract echocardiogram image textural properties within the myocardium. These studies have unveiled further useful details of carotid artery and myocardium compared to the previous manual and semi-automated techniques. Wavelet based methods (DWT [158, 164, 165, 171, 173, 176, 182], SWT [175]) and HOS [180, 181] have shown to extract most of the information including subtle changes, occurring in the carotid artery and myocardium with significantly high accuracies. Furthermore, LBP and LCP methods, applied on the echocardiogram images, can identify the minute variations in the myocardium and thereby classify them into moderately and severely infarcted myocardium [174].

However, it is also evident from the literature survey that only few studies have used computer aided methods to support the diagnosis for CAD and carotid atherosclerosis using IVUS. Other than Araki et al. and Nair et al., not much research work is reported on CAD and carotid atherosclerosis using computer-aided analysis of IVUS images. Araki et al., [32] used grayscale features to analyse the texture properties of IVUS images to identify the CAD risk stratification. Nair et al., [183] performed spectral analysis of IVUS images for real time in vivo plaque classification [183]. Although the first-order [32] and time-frequency domain [183] texture analysis techniques achieved good results in the identification of CAD [32] and carotid atherosclerosis [183], second-order statistics, HOS, DWT, and other nonlinear methods can substantially improve the performance of computer support systems based on IVUS images. These methods may extract additional higher-order and phase information from IVUS image texture, compared to first-order and linear methods with better accuracy and may even aid in identifying the severity of the conditions.

The most important aspect of expert systems, such as computer aided diagnosis, is to replace human labour with machine work [185]. Through mass production, it is possible to harvest the economies of scale, which brings down the unit price and revenue is generated via sales volume. However, there is an inherent danger in this approach, namely the problem of monoculture. To be specific, mass produced systems tend to be well engineered, but their number may become so large that even small probabilities for an individual safety failure can become a major concern [186]. Safety concerns are important aspects for computer support in medicine [187]. As described in materials section, the offline system is used to establish the functionality aspects of a proposed system. The performance measures, reported in Tables 1, 2 and 3, the system performance under well controlled conditions. However, mass production and subsequent mass deployment demand considerations on how to ensure reliability and safety. These considerations are challenging, because safety is a multifaceted concept. One of these facets is active safety [188]. For example, a diagnosis, suggested by the computer system must be confirmed by the clinician. Another aspect passive safety [189], which demands that safety critical system failures must be kept at a minimum. The only way to meet the required passive safety levels is to improve the design process. Splitting the design into online and offline systems is one step in the right direction. However, the concept of having an online and an offline system is not sufficient to achieve the required passive safety levels, because the design steps, described in Section 3, are only concerned with requirements capturing. With the offline system we find out what system we are going to build. To design safe and reliable systems, we need another step, namely specification refinement. In other words, we need to find out how we build the system. The specification refinement step must be executed as formal as possible, because logical errors in this step may impact negatively on passive safety. Formal logic can be used to ensure that no setting in the user interface has an impact on the system functionality which might compromise patient wellbeing [190, 191].

The considerations outlined above, lead to the postulation of the formal and model driven design methodology for biomedical systems [192]. The design steps follow the systems engineering meta model: need definition, requirements capturing – with the offline system, implementation of the online system, deployment and decommissioning [193]. In the specification refinement phase, formal methods, such as Communicating Sequential Processes (CSP) [194], B-method [195] and petri nets, can be used to establish beyond reasonable doubt specific safety and reliability aspects of the diagnosis support system [196].

5.1. Future Work

The following list introduces areas for future work:

- Deep learning concept can be used extract features and improve the decision making performance of computer aided diagnosis systems.

- The accuracy of cardiovascular disease diagnosis, based on US images, may improve by segmenting the ROI and extracting features from these ROIs. More work is needed to segment the ROI from IVUS and US images without losing much information.

- Although the MI detection algorithms (DWT, HOS, Textons, LCP), proposed by Sudarshan et al., achieved high accuracy, similar investigation need to be carried out for diagnosis of CAD using IVUS [174].

- IVUS and US images are associated with high speckle noise [197, 198]. Therefore, an efficient algorithm for speckle noise reduction as a preprocessing technique before the feature extraction may improve the performance of the computer aided diagnosis.

- Using computer-aided methods, there is a possibility of exploring the detection of mild stage of MI using US images; similarly, the extent of CAD can be detected using IVUS.

- Carotid atherosclerosis diagnosis may benefit from automating the ROI segmentation. Such automation can help to improve the classification accuracy of asymptomatic plaque.

We predict that the role of computer aided diagnosis will continue to expand at an accelerating speed. Once the systems are designed, they can be mass produced with minimum cost. Furthermore, hardware and software updates can be used to incorporate the latest research results from relevant fields of medicine and technology in an installed system. At the moment, we are at an early stage of such a design revolution. By using a meta model, which structures the design process into an online and an offline system, we have the flexibility to explore novel research on algorithms even if the online system is already deployed. The offline design process will look more and more like a big data task where algorithms inspect huge data and extract useful information from the training images. These tasks will be executed with an ever-increasing level automation and the processing will migrate towards virtualized bulk processing environments, such as cloud computing [199]. As a consequence, local processing and decision making will be superseded by distributed processing systems incorporating the latest information in the decision-making process.

6. Conclusion

This paper reviews computational and system design aspects of computer support for cardiovascular disease diagnosis based on US images. Initially we provided background information on CAD, MI and carotid atherosclerosis. The three investigated diseases are linked. CAD usually precedes MI and carotid atherosclerosis is a good indicator of plaque in the coronary arteries. A major problem for the design of such systems comes from the fact that it is impossible to know a priori which algorithm structure works best for a given problem. Therefore, the design process follows a well-defined meta model which structures the design efforts into creating an offline and an online system. The offline system is used to research, assemble and test a wide range of algorithm structures. Only the best algorithms are used in the online system to provide the best possible diagnostic support for practitioners. Hence, the key concept during the design of diagnostic support systems is competition facilitated through quality measurements. Consequently, we reviewed several algorithms used in the proposed diagnosis support systems and presented their performances.

During the review, we placed emphasis on discriminating between basic analysis systems and computer aided diagnosis systems. We found that, there is many thoracic US based systems which provide diagnostic support through artificial decision making. In contrast, only one IVUS based system provided that type of support. The rest of the reviewed IVUS based systems provided only clinical analysis. Such analytical support is important; data analysis has progressed more towards diagnostic support. Therefore, the next logical step for IVUS based computer support systems is to incorporate a classification step. The resulting computer aided diagnosis systems will be more useful as they can improve the diagnosis quality and traceability. Another important point of this review is that IVUS is predominantly used for automated CAD diagnosis. In contrast, thoracic US is most often used for MI diagnosis support systems. IVUS is used for post-mortem analysis of carotid plaque and specialized carotid artery assessment. However, that imaging methodology is considered unsuitable for screening applications.

Acronyms

A Accuracy

AI Artificial Intelligence

ANOVA Analysis Of Variance

BPSO Binary Particle Swarm Optimization

CAD Coronary Artery Disease

CSP Communicating Sequential Processes

CT Curvelet Transform

DT Decision Tree

DWT Discrete Wavelet Transform

ECG Electrocardiography

GA Genetic Algorithm

GLCM Gray-Level Co-occurrence Matrix

GMM Gaussian Mixture Model

HOS Higher Order Spectra

I Internal

IVUS Intravascular Ultrasound

K-NN K-Nearest Neighbour

LBP Local Binary Pattern

LCP Local Configuration Pattern

LRNC Lipid-Rich Necrotic Core

MI Myocardial Infarction

NBC Naive Bayes Classifier

PCA Principal Component Analysis

PNN Probabilistic Neural Network

RBF Radial Basis Function

ROI Region of Interest

RVM Relevance Vector Machine

SWT Stationary Wavelet Transform

SCD Sudden Cardiac Death

Se Sensitivity

SOM Self Organizing Map

Sp Specificity

SVM Support Vector Machine

T Thoracic

TIA Transient Ischemic Attack

US Ultrasound

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