Artificial Intelligence in
Medical Imaging

Contents

ABOUT COVER

Editor-in-Chief of *Artificial Intelligence in Medical Imaging*, Professor Xue-Li Chen is an expert in the field of biomedical photonics imaging as well as its application in early detection and accurate diagnosis of gastric cancer. Professor Chen has co-led the development of Cerenkov luminescence endoscope and further explored the application in early detection of clinical gastrointestinal tumors. Professor Chen has also developed the stimulated Raman projection tomography technology which can perform the volumetric imaging of single cells in a label-free manner. Professor Chen has served as the member of SPIE, OSA, IEEE, and as a committee member of the Branch of Contrast Technology in China Medicinal Biotech Association, the Nuclear Medicine Committee of Shaanxi Cancer Association, and the Shaanxi Society of Biomedical Engineering.

AIMS AND SCOPE

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INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Machine learning for diagnosis of coronary artery disease in computed tomography angiography: A survey

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Abstract

Coronary artery disease (CAD) has become a major illness endangering human health. It mainly manifests as atherosclerotic plaques, especially vulnerable plaques without obvious symptoms in the early stage. Once a rupture occurs, it will lead to severe coronary stenosis, which in turn may trigger a major adverse cardiovascular event. Computed tomography angiography (CTA) has become a standard diagnostic tool for early screening of coronary plaque and stenosis due to its advantages in high resolution, noninvasiveness, and three-dimensional imaging. However, manual examination of CTA images by radiologists has been proven to be tedious and time-consuming, which might also lead to intra- and interobserver errors. Nowadays, many machine learning algorithms have enabled the (semi-)automatic diagnosis of CAD by extracting quantitative features from CTA images. This paper provides a survey of these machine learning algorithms for the diagnosis of CAD in CTA images, including coronary artery extraction, coronary plaque detection, vulnerable plaque identification, and coronary stenosis assessment. Most included articles were published within this decade and are found in the Web of Science. We wish to give readers a glimpse of the current status, challenges, and perspectives of these machine learning-based analysis methods for automatic CAD diagnosis.

Key words: Machine learning; Deep learning; Coronary artery disease; Atherosclerotic plaque; Vulnerability; Stenosis; Segmentation; Computed tomography angiography

Core tip: There are reviews that contributed to the segmentation of the coronary artery, detection of calcified plaques, and calculation of fractional flow reserve. To the best of our knowledge, this is the first paper to survey the machine learning algorithms for the diagnosis of coronary artery disease in computed tomography angiography images, including extraction of coronary arteries, detection of calcified, soft and mixed plaques, identification of plaque vulnerability features including low density plaque, positive remodeling, spot calcification, and napkin ring sign, assessment of both anatomically and hemodynamically significant stenosis, and the challenges and perspectives of these machine learning-based analysis methods.

INTRODUCTION

Coronary artery disease (CAD) has become a major illness endangering human health, which caused more than 17.6 million deaths worldwide in 2016[1]. Atherosclerotic plaque is the pathological basis of CAD, especially vulnerable plaques without obvious symptoms in the early stage. Once a rupture occurs, it will lead to severe coronary stenosis, which in turn may trigger a major adverse cardiovascular event[2]. Therefore in CAD diagnosis, it is urgent to accurately detect coronary plaques, identify their vulnerable features, and assess the resulting stenosis. Computed tomography angiography (CTA) has become a standard diagnostic tool for early screening of CAD due to its advantages in high resolution, noninvasiveness, and three-dimensional (3D) imaging[3]. However, manual examination of CTA images by radiologists has been proven to be tedious and time-consuming, which might also lead to intra- and interobserver errors[4].

To date, many state-of-the-art machine learning (ML) algorithms have enabled the (semi-)automatic diagnosis of CAD by extracting quantitative features from CTA images. These ML algorithms can be grouped into: (1) Conventional ML algorithms that are typically based on the predefined or hand-crafted features, such as linear regression, support vector machine (SVM), and random forests; and (2) Deep learning (DL) algorithms that can directly learn features from original medical images, such as the convolutional neural network (CNN) and recurrent neural network.

There are some reviews that contributed to the segmentation of the coronary artery[5], detection of calcified plaques[6], and calculation of fractional flow reserve (FFR) with both the rule-based (non-ML) and ML-based methods[7]. This paper provides a survey of the above two groups of ML methods in (semi-)automatic diagnosis of CAD, including coronary artery extraction, coronary plaque detection, vulnerable plaque identification, and coronary stenosis assessment (Figure 1 and Table 1). Most included articles were published within this decade and appear in the Web of Science. Instead of exhaustively listing all of the ML methods of coronary plaque diagnosis, we focus on typical ML-based methods with CTA images in recent years and summarize the challenges regarding these methods.

CORONARY ARTERY EXTRACTION

Due to the tortuous structure of the coronary arteries, it is necessary to perform multiplanar reconstruction or curved planar reconstruction visualization of CTA images before CAD diagnosis[8]. The reconstruction of both multiplanar reconstruction and curved planar reconstruction images relies on the extraction of coronary artery trees. In addition, some studies have directly carried out a plaque analysis along the cross-section perpendicular to the coronary artery[9,10]. It can be seen that the accurate extraction of coronary arteries plays an indispensable role in CAD diagnosis. Manual

Table 1 Summary of different machine learning-based methods used in coronary artery disease diagnosis

CAD diagnosis	Method	Task	Category
Coronary artery extraction			
Schaap *et al*[14]	Linear and nonlinear regression	Artery	ML
Huang *et al*[15]	3D U-net	Artery	DL
Kong *et al*[16]	ConvRNN + ConvGRU	Artery	DL
Shen *et al*[17]	3D FCN + level set	Artery	DL
Wu *et al*[18]	CNN + nearest neighbor search	Artery	DL
Wolterink *et al*[19]	3D dilated CNN	Centerline	DL
Coronary plaque detection			
Mittal *et al*[20]	PBT, RF	Calcified	ML
Kurkure *et al*[21]	SVM	Calcified	ML
Wei *et al*[22]	Linear discriminant analysis	Soft	ML
Jawaid *et al*[23]	SVM	Soft	ML
Tessmann *et al*[24]	AdaBoost	Multiple	ML
Kelm *et al*[25]	PBT, RF	Multiple	ML
Zhao *et al*[26]	SVM	Multiple	ML
Zreik *et al*[27]	CNN + RNN	Multiple	DL
Huo *et al*[28]	Attention recognition dual network	Calcified	DL
Vulnerable plaque identification			
Kolossváry *et al*[33]	Radiomics	NRS	ML
Kolossváry *et al*[2]	Radiomics	LAP &NRS	ML
Kolossváry *et al*[34]	Logistic regression, K-nearest neighbors, RF, least angle regression, naive Bayes, Gaussian process classifier, decision trees, DNN	Advanced lesion	ML, DL
Coronary stenosis assessment			
Zuluaga *et al*[36]	SVM	ASS	ML
Kang *et al*[37]	SVM + formula-based analytical method	ASS	ML
Zreik *et al*[27]	CNN + RNN	ASS	DL
Itu *et al*[41]	DNN	HSS	DL
Wang *et al*[42]	DeepVessel-FFR	HSS	DL
Dey *et al*[43]	Boosted ensemble algorithm	HSS	ML
Kumamaru *et al*[44]	2D conditional generative adversarial network + 3D convolutional ladder network	HSS	DL

ASS: Anatomically significant stenosis; CAD: Coronary artery disease; CNN: Convolutional neural network; ConvGRU: Convolutional gated recurrent unit; ConvRNN: Convolutional recurrent neural network; DL: Deep learning method; DNN: Deep neural network; FCN: Fully convolutional network; FFR: Fractional flow reserve; HSS: Hemodynamically significant stenosis; LAP: Low density plaque; ML: Conventional machine learning method; NRS: Napkin ring sign; PBT: Probability boosting tree; RF: Random forest; RNN: Recurrent neural network; SVM: Support vector machine.

extraction of the coronary arteries is labor intensive and observer dependent. Therefore, automatic/semi-automatic extraction methods have been adopted, such as the Hessian matrix method, mathematical morphology, and minimal cost path[5,11]. These traditional methods discriminate coronary arteries from the background based on intuitively and exquisitely designed models[12].

ML methods transfer the segmentation into the problem of pixel classification by assigning each pixel as the coronary artery or background[13]. Specifically, Schaap *et al*[14] employed both linear regression and nonlinear regression to learn the arterial geometry and appearance from annotated CTA images, and then made full use of the
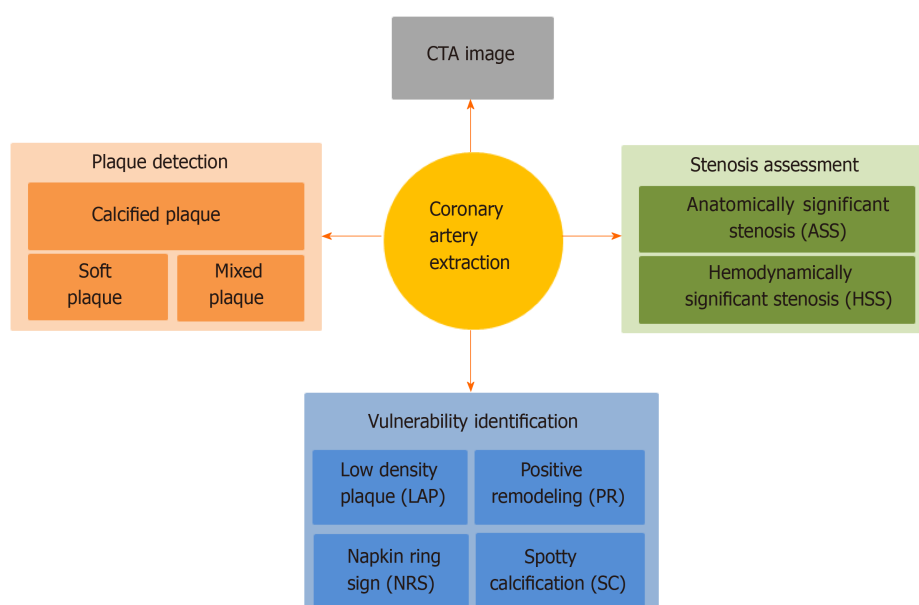
Figure 1 Main topics of this survey, including coronary artery extraction, coronary plaque detection, vulnerable plaque identification, and coronary stenosis assessment. CTA: Computed tomography angiography.

learned knowledge to segment coronary arteries in unseen CTA images. Huang *et al*[15] introduced the 3D U-net, a typical fully convolutional network (FCN), to segment the coronary artery, which densely performed the pixel-wise classification *via* directly extracting features from CTA images. Alternatively, Kong *et al*[16] employed a convolutional recurrent neural network and a tree-structured convolutional gated recurrent unit to learn the anatomical structure of the coronary artery, and hereby they achieved accurate segmentation of coronary arteries. Recently, the combination of traditional methods (such as level set and nearest neighbor search) and DL methods (such as fully convolutional network and CNN) were also devised for coronary artery segmentation[17,18]. Moreover, Wolterink *et al*[19] trained a 3D dilated CNN to iteratively track the centerline points in CTA images in which the coronary artery could be reconstructed based on the extracted centerline and the radius of each centerline point.

CORONARY PLAQUE DETECTION

Depending on the degree of calcification, coronary plaques can be divided into calcified plaques (full calcification), soft plaques (no calcification), and mixed plaques (partial calcification). Mittal *et al*[20] used probability boosting trees and random forests to detect coronary calcified plaques with the designed rotation invariant features along the coronary centerline. Kurkure *et al*[21] adopted an SVM-based method to detect the calcification positions in the aorta and coronary arteries, amongst which they selected coronary calcified plaques. Wei *et al*[22] proposed a topological soft gradient pre-screening method to obtain candidate soft plaques and then detected soft plaques from the candidate set by a linear discriminant analysis. Jawaid *et al*[23] divided the coronary cross-section into eight concentric circles. Then they constructed an SVM to identify abnormal coronary segments caused by soft plaques based on the difference in strength stability and localized and identified soft plaques. However, due to large morphological differences between different types of plaques, it is challenging to simultaneously detect multiple types of coronary plaques.

Thus, Tessmann *et al*[24] performed feature extraction on a cylindrical coronary region of interest and introduced the AdaBoost algorithm to identify calcified plaques and soft plaques. Kelm *et al*[25] regressed the vessel radius based on the pre-acquired centerline to evaluate stenosis and then constructed a classifier (similar to[20]) to determine the type of coronary plaques that caused the stenosis, so as to realize the classification of multiple types of plaques. Zhao *et al*[26] designed a random radial symmetric feature vector and augmented the training data by rotating the cross-section with random angles. Then they trained an SVM to detect and classify

multiclass coronary plaques. With the advantages in representing the complex texture of medical images, DL methods have been brought to the domain of plaque image analysis. Zreik *et al*[27] constructed a CNN model to extract the image features of coronary artery sections, and then used a recurrent neural network to fuse the features extracted by multiple CNNs. Finally, they realized the detection and classification of different coronary plaques. Huo *et al*[28] proposed a weak supervised attention recognition dual network to perform the detection of calcified plaques, which required only scan-level labels instead of pixel-level labels.

VULNERABLE PLAQUE IDENTIFICATION

CTA imaging can evaluate plaque components in coronary arteries with the diameter greater than 1.5 mm[29]. Studies found that the plaque vulnerability in CTA images was closely related to low density plaque, positive remodeling, spotty calcification, and napkin ring sign (NRS)[30,31]. If a coronary plaque contains two or more of the above four vulnerable features, the plaque is more likely to be a vulnerable plaque[32]. Traditionally, visual inspection performed by radiologists is used to determine whether a coronary plaque contains the above vulnerable features. However, different patients have large individual differences in CTA imaging, resulting in the visual inspection relying heavily on experienced radiologists.

ML-based radiomics can extract a large number of quantitative features from the image to describe the complex texture and spatial structure of the lesion area, providing an automated solution for plaque vulnerability analysis. Kolossváry *et al*[33] applied radiomics to the identification of NRS in coronary CTA images, and the results showed that radiomic features were superior to traditional imaging parameters in distinguishing NRS and non-NRS plaques. Afterwards, they identified the low density plaque, NRS, and $Na^{18}F$-positive vulnerable features in CTA images[2]. The results demonstrated that noninvasive CTA diagnosis could accurately distinguish high risk plaques that were previously diagnosed by intravascular ultrasound, optical coherence tomography, and positron emission tomography. In addition, they also collaborated with researchers from the Massachusetts General Hospital to identify advanced coronary atherosclerotic lesions through an ML-based radiomics analysis of *ex vivo* coronary CTA imaging[34]. The identification results on the cross-section were better than the visual inspection and histogram evaluation.

CORONARY STENOSIS ASSESSMENT

Various types of plaques are the main causes of coronary stenosis, *i.e*. narrowing of the coronary artery lumen, which will restrain blood flow to the myocardium and potentially lead to myocardial ischemia[35]. Therefore, the assessment of coronary stenosis is also an important aspect in the diagnosis of CAD. Taking physiology into account, coronary stenotic lesions are generally categorized as anatomically significant stenosis and hemodynamically significant stenosis, both of which can be noninvasively assessed by CTA imaging. Anatomically significant stenosis refers to the narrowing of the coronary lumen of at least 50%, which acts as the early assessment for the severity of stenosis in CAD patients. Zuluaga *et al*[36] employed SVM to detect coronary stenosis and arterial bifurcation based on the features of concentric circles in two-dimensional cross-sectional images. Kang *et al*[37] developed a structured learning algorithm based on SVM and a formula-based analytical method to detect both obstructive (with over 50% stenosis) and non-obstructive (with stenosis between 25% and 50%) lesions. Furthermore, Zreik *et al*[27] applied a recurrent CNN on coronary artery multiplanar reconstruction images to detect different grades of anatomically significant stenosis, including no stenosis, nonsignificant stenosis (with less than 50% narrowing), and significant stenosis (with over 50% narrowing). However, the detected anatomically significant stenosis from CTA images has only moderate specificity for predicting hemodynamically significant stenosis (HSS) that causes myocardial ischemia[38].

Currently, FFR is the standard examination for diagnosis of HSS, which invasively measures the ratio of distal blood flow to the proximal blood flow of the stenosis by inserting a special catheter. FFR estimation based on CTA images (FFT_{CT}) provides a noninvasive alternative for evaluating HSS based on computational fluid dynamics[39,40], which is accurate but computationally demanding due to the complex iterative computation. To improve the computation efficiency, Itu *et al*[41] proposed an

artificial neural network to predict the FFR value of each coronary artery segment based on the geometry and global features extracted from the most severe stenosis. Wang *et al*[42] developed a DL method (DEEPVESSEL-FFR) to calculate the FFR value from CTA images and predicted the ischemic risk of HSS. Both of the above ML-based FFR prediction methods only rely on the geometry of the coronary artery, leading to their susceptibility to the errors of coronary artery segmentation. Therefore, Dey *et al*[43] performed the HSS identification with a boosted ensemble algorithm, which combined the geometric features of stenosis with the volumes of plaques, the contrast density difference, and the plaque length. Moreover, Kumamaru *et al*[44] proposed a 3D DL model to identify patients with at least one HSS, where the model could automatically extract the representative features from the CTA dataset without segmentation or other data manipulation.

CHALLENGES AND PERSPECTIVES

ML algorithms have been widely used in the analysis of CTA images for CAD diagnosis, including the extraction of coronary arteries, diagnosis of plaques, and assessment of stenotic lesions. In particular, DL methods can directly extract task-specific features from input CTA images, which have partially replaced conventional ML methods that depend on the hand-crafted features (or engineered features). Nevertheless, there are some merits and challenges for both the conventional ML methods and DL-based methods. (1) Conventional ML methods are more often involved in plaque and stenosis diagnosis, where the used hand-crafted features were designed according to the visual and clinical experience of radiologists. For this reason, the diagnostic results of these ML methods are inherently explainable, which means they can explicitly show task-relevant quantitative features. Moreover, these ML models are relatively simple and easy to train with only a small number of CTA images. However, the quantitative features used in the ML methods heavily depend on the careful designing by computer vision experts. How to develop or select task-specific quantitative features requires extensive experience accumulation; and (2) DL-based methods are sometimes applied in both coronary artery extraction, and stenosis and plaque diagnosis. DL methods can integrate the whole ML-based analysis workflow including (hand-crafted) feature extraction, feature selection, and classifier training into only one DL model, whose performance would be continuously improved *via* end-to-end learning as long as enough training samples are provided[45]. However, DL methods generally require a large number of training samples. As is known, manual labeling of coronary data is time-consuming and laborious, so the number of labeled samples is still very limited, even though there are large amounts of patient data in the clinics. Moreover, difficulty in interpretability may also prevent using the DL methods in clinical diagnosis of CAD.

Nevertheless, the DL method has become an important branch in the family of ML algorithms, especially for coronary artery segmentation and coronary stenosis assessment. It is foreseeable that most tasks in CAD diagnosis may start using DL methods or at least the combination of DL and conventional ML methods. For the latter, the DL method functions like a feature extractor, and the classifier from the conventional ML method carries out the subsequent classification. There are some solutions that may address the shortcomings of DL methods. For example, semi-supervised DL methods in natural image processing can potentially solve the classification with only small labeled data. It is reported the prediction error of semi-supervised methods using only 4000 labeled samples in the CIFAR-10 dataset was approximated to supervised learning with 50000 labeled samples[46,47]. Moreover, some studies tried to explain the decision made by a DL model by double-checking the results with an expert[48], generating a heat-map to highlight the input regions responsible for a specific task[49], or projecting the high-dimensional feature space to a bi-dimensional plane[50].

CONCLUSION

In conclusion, we have surveyed the ML-based CAD diagnostic methods in CTA images in recent years and highlighted the most typical application of both conventional ML and DL methods. We wish to give the readers a glimpse of the current status, challenges, and perspectives of these ML-based analysis methods for automatic CAD diagnosis.

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