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Artificial intelligence for advanced analysis of coronary plaque

Marly van Assen[1,2], Philipp von Knebel Doeberitz[1,2,3], Arshed A. Quyyumi[4], and Carlo N. De Cecco[1,2]*

[1]Department of Radiology and Imaging Sciences, Emory University, Inc. 1365 Clifton Road NE, Suite—AT503, Atlanta, GA 30322, USA; [2]Translational Laboratory for Cardiothoracic Imaging and Artificial Intelligence, Emory University, Atlanta, GA 30322, USA; [3]Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; and [4]Division of Cardiology, Department of Medicine, Emory University, Atlanta, GA 68167, USA

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The field of coronary plaque analysis is advancing including more quantitative analysis of coronary artery diseases such as plaque burden, high-risk plaque features, computed tomography-derived fractional flow reserve, and radiomics. Although these biomarkers have shown great promise for the diagnosis and prognosis of cardiac patients in a research setting, many of these advanced analyses are labour and time intensive and therefore hard to implement in daily clinical practice. Artificial intelligence (AI) is playing an increasing role in supporting the quantification of these new biomarkers. AI offers the opportunity to increase efficiency, reduce human error and reader variability and to increase the accuracy of diagnosis and prognosis by automating many processing and supporting clinicians in their decision-making. With the use of AI these novel analysis approaches for coronary artery disease can be made feasible for clinical practice without increasing cost and workload and potentially improve patient care.

Introduction

Artificial intelligence (AI) is rapidly advancing in the healthcare sector. In 2020, AI applications across the healthcare market were estimated to be valued at 4.9 billion dollars in the US alone with an estimated growth to $45.2 billion by 2026. Medical imaging can especially benefit from the use of AI. The development of convolution neural networks (CNN), a type of deep learning algorithm ideally suited to deal with imaging data, and the increasing availability of medical imaging data have greatly supported the creation of imaging-dedicated AI algorithms. Over 300 AI applications are currently approved by the FDA in the radiology and cardiovascular fields.[1] In cardiac imaging, AI technologies are expected to increase diagnostic accuracy by increasing rates of detection of abnormalities, permitting better characterization of cardiovascular disease and optimization of the clinical workflow by contributing to scheduling, protocol selection and reconstruction and post-processing of images.

Cardiovascular disease is one of the leading causes of death globally, the majority of which are due to coronary artery disease (CAD), with atherosclerosis being the main process driving the risk of adverse events. Coronary computed tomography angiography (CCTA) offers a non-invasive approach to evaluate CAD with very high accuracy for the detection of CAD and is now clinically well integrated. With increasing support for CCTA as a class I indication for the evaluation of stable chest pain in the new guidelines,[2] the demand for cardiac imaging is on the rise. CAD imaging has traditionally focused on the evaluation of coronary stenosis severity even though revascularization of obstructive stenoses has failed to consistently improve prognosis.[3] There are several imaging biomarkers of coronary atherosclerosis besides stenosis severity that appear to be more indicative of high-risk

*Corresponding author. Tel: +1 404 778 4876, Email: carlo.dececco@emory.edu

anatomy and can help improve risk prediction and guide treatment. The magnitude of plaque burden is a superior predictor of thrombotic events than stenosis grading alone, with the risk of rupture increasing with higher plaque burden.[4] Coronary artery calcium (CAC) scoring using CT offers the simplest method of assessing plaque burden. However, statin therapy may result in an increase in CAC that prevents its use as a method for longitudinal assessment of plaque burden. There is increasing evidence that plaque composition, in addition to plaque burden, plays a pivotal role in mediating the risk of adverse events, indicating that phenotyping of high-risk plaques (HRP) that are unstable and vulnerable to rupture is critical in identifying those that are responsible for acute coronary syndromes (ACS) and myocardial infarction.[5]

Emerging invasive and non-invasive imaging technologies enable the identification of plaque components and HRP features. Although intravascular ultrasound (IVUS) has traditionally been used for plaque morphological analysis, recent advances in CCTA enable accurate and simultaneous assessment of stenosis severity, plaque burden, and HRP features.

Adipose tissue parameters, indicative of early stage atherosclerosis, include epicardial (EAT) and peri-coronary adipose tissue (PCAT) quantification. In addition, it is hypothesized that inflammation is related to active more vulnerable plaque and can therefore be used to identify HRP.[6] In addition to these morphological plaque features, the functional significance of coronary plaque has proven to be a more accurate predictor of adverse events. Fractional flow reserve (FFR) is currently recommended to assess the functional significance of coronary artery stenosis, however, FFR is an invasive, costly, and time-consuming procedure. AI has paved the way to calculate CT-derived FFR, a measure of flow reduction caused by coronary stenoses, without the need for time-consuming extensive computations.

With increasing interest in these quantitative biomarkers comes an increase in manual labour to perform all the analysis involved, challenging making clinical implementation in a field that is already suffering a massive increase in workload. AI can help in making these biomarkers clinically accessible by assisting in data extraction and by automation of preprocessing and data analysis. In addition, with the help of AI, it is possible to combine information of the electronic medical records with imaging biomarkers to further personalize and improve risk stratification and prognostication.

Coronary plaque detection and stenosis severity quantification

One of the main applications of CT in CAD imaging is the detection of coronary plaque and the quantification of stenosis severity by utilizing a combination of CAC assessment and CCTA.

Coronary artery calcium

Quantification of CAC, a relatively simple procedure, is recommended by several international guidelines for the detection and risk assessment of CAD.[7] The CAC score serves as an indirect measure of plaque burden and is a strong predictor of incident adverse events. CAC scoring can be readily automated and AI-based CAC scoring has excellent accuracy when compared to expert readings and can be obtained accurately in a fraction of the time, thus improving clinical workflow, *Figure 1*(*A*). CAC scoring is traditionally performed on ECG-triggered non-contrast acquisitions. However, chest CT imaging for other indications offers an opportunity for incidental CAC scoring that can be achieved using AI on non-ECG-triggered non-cardiac examinations, thus expanding the availability of cardiovascular risk assessment.

CCTA and CAD-RADS 2.0

CCTA is required for the detection and classification of coronary artery stenoses as it has a high negative predictive value for the exclusion of CAD that is found in almost 50% of patients currently. In patients with CAD, CCTA permits grading of the severity of lesions and identification of obstructive lesions that might benefit from intervention. Even individuals with non-obstructive CAD (<50% stenosis) have worse outcomes (event rate ~1.6%) compared to those without CAD (event rate 0.2%).[8] The CAD-RADS™ system was designed to standardize reporting of CAD stenosis severity and enhance multidisciplinary communication. This system classifies stenosis severity in predefined categories paired with follow-up recommendations: (CAD-RADS 0 = no atherosclerosis; CAD-RADS 1–2 = non-obstructive disease present; CAD-RADS 3–5 = obstructive disease).[9] However, manual CAD-RADS reading is more complex than CAC scoring, can be time consuming and is prone to inter-reader variability and is susceptible to differences between centres and in reporting practices. Augmentation of CAD-RADS evaluation using AI-based software can form the cornerstones of coronary artery segmentation, stenosis detection, and severity analysis. Dedicated algorithms are currently under development, with initially promising results, that can assist radiologists in determining CAD-RADS with higher accuracy and reduced reading time and variability, *Figure 1*(*B*) and (*C*). CAD-RADS 2.0 now recommends reporting of HRP and plaque burden,[9] that can be assisted by AI-based software innovation. AI-assisted plaque burden quantification, normally time intensive and subject to inter-reader variability, is being developed. Nevertheless, CCTAs are complex exams and further evaluation is needed for the analysis of coronary anomalies, myocardial bridging, and imaging artefacts.

Morphological plaque features

In addition to detecting coronary plaque, CCTA permits the evaluation of morphological and functional characteristics of the plaque, such as plaque burden and composition that aid in the prognostication of CAD.

High-risk plaque features

Histological assessment of coronary atherosclerosis has identified a set of HRP features that characterize culprit lesions responsible for ACS and include thin-cap fibroatheroma, large plaque volume, and necrotic core.[10] These features can be identified using invasive imaging methods including IVUS, optical coherence tomography and near-infrared spectroscopy, or non-invasively using CCTA. CCTA allows identification of both calcified and non-calcified plaque, determination of plaque size and specific HRP features including low attenuation plaque (<30HU), napkin

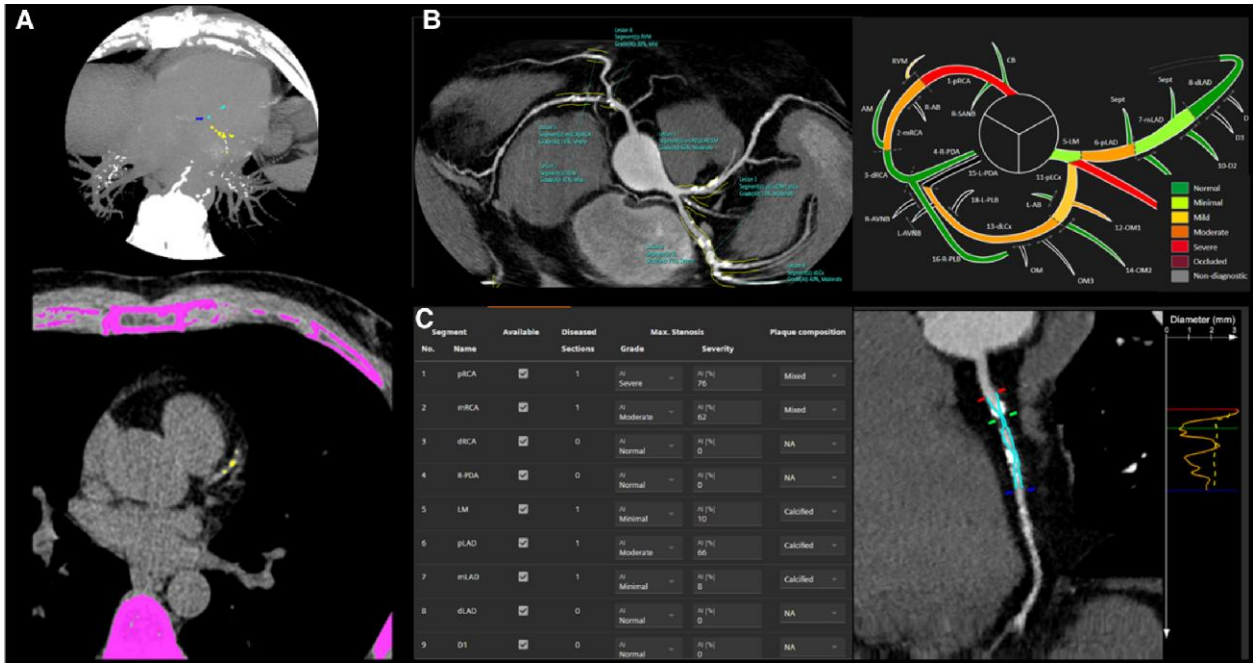

Figure 1 AI algorithms for CAC Agatston score, CCTA plaque detection, and automated CAD-RADS classification. (*A*) showing an AI-based coronary calcium scoring (Siemens Healthineers). (*B*) The AIHeart algorithm (Siemens Healthineers) is a prototype that allows CAD-RADS classification by identification and classification of coronary plaque. (*C*) shows the AIHeart results for all coronary segments and lesions including stenosis degree and plaque composition, with options for manual correction.

ring sign, positive remodelling, and spotty calcifications, entities that are more frequently found in culprit lesions associated with ACS and adverse clinical outcomes.[8]

Manual segmentation and identification of coronary plaque and HRP features is very labour intensive and therefore impractical for clinical deployment. Recent advances in several AI-augmented software programmes that automatically perform quantitative plaque analysis, permits reproducible quantification of plaque burden, identification and quantitation of calcified and non-calcified plaque, detection of HRP features including positive remodelling and determination of stenosis severity.[11] Many of these AI-assisted software programmes have been successfully validated using IVUS measurements or histology data from carotid plaques.[11]

Plaque burden and progression

The total coronary plaque burden is an indicator of disease severity and more accurately predicts outcomes compared to stenosis severity assessments.[12] In addition, non-calcified plaque burden that identifies more vulnerable or active plaque, can also be detected by CCTA, allowing more accurate prognostication. AI permits rapid and more standardized analysis of plaque burden (*Figure 2*). Coronary atherosclerosis usually progresses over time although the rate of progression can vary widely. Quantification of CAD progression can play a crucial role in improving prognostication and can be utilized to assess the effectiveness of anti-atherosclerotic therapies and to guide treatment decisions. Although serial CT imaging enables longitudinal evaluation of plaque progression, there are concerns regarding the consistency of CT imaging protocols and systems that complicate interpretation. The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging) study,[13] conducted serial CCTA 3.8 years apart in 1225 patients, highlights the value of CT for the evaluation of plaque progression and determination of the impact of lipid-lowering intervention AI-based plaque quantification methods can aid evaluation of large patient populations, more accurate determination of relatively small changes in plaque burden and reduce the variability of measurements (*Figure 2*).

Functional measures

Computed tomography-fractional flow reserve

While CCTA is known for the assessment of morphological features of coronary plaque, functional assessments that determine flow consequences of CAD appear to have additional value in risk stratification. FFR assesses the haemodynamic significance of coronary stenoses and is traditionally assessed during coronary angiography using invasive methods. It is now to perform FFR analysis coronary CT images. CT-derived FFR (CT-FFR_{CFD}, Heartflow Inc.) employs computational fluid dynamics (CFD) and to date is the only FDA-approved method. However, there are several machine learning-based CT-FFR applications that are available and allow rapid in-house calculation of CT-FFR with high accuracy when compared to invasive FFR and CFD-based FFR,[14] *Figure 3*. The use of CT-FFR allows simultaneous anatomical and functional assessments and can thereby improve the prognostication.

Adipose tissue

Inflammation plays a key role in the development and progression of CAD. Although stenosis assessment and plaque analysis play a major role in the evaluation of CAD, 10% of

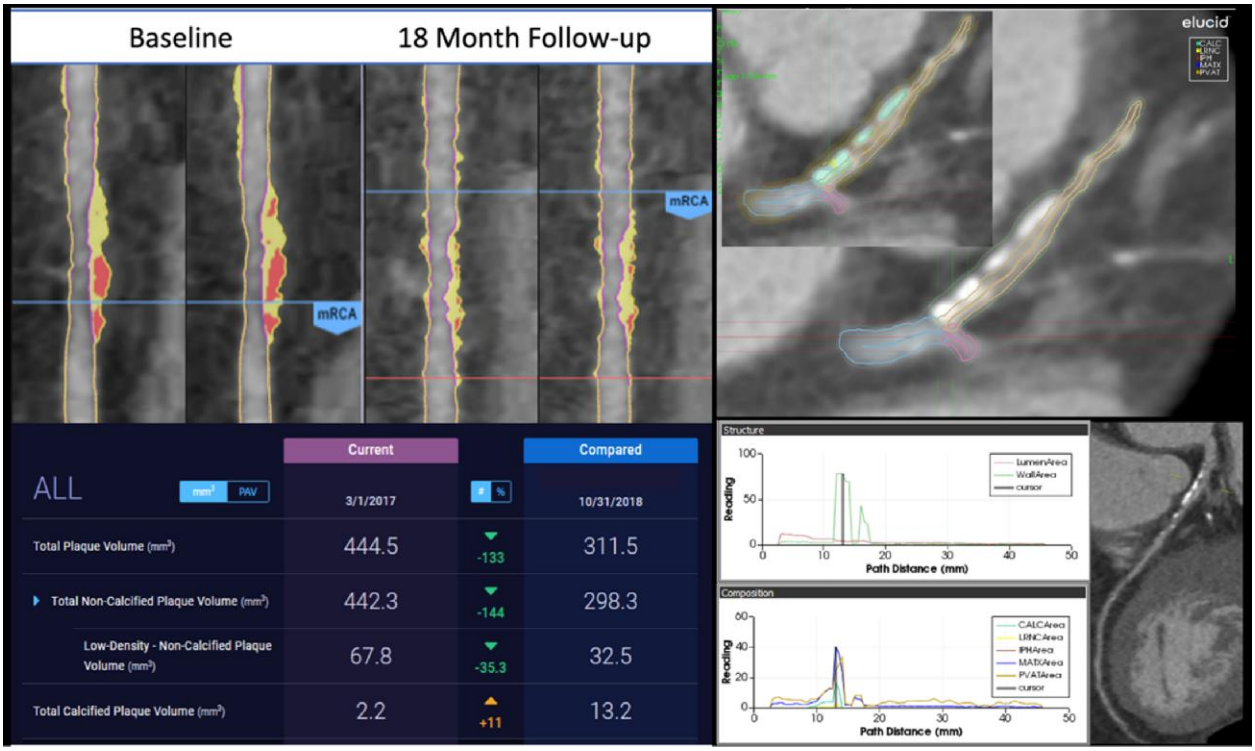

Figure 2 AI algorithms for advanced CCTA plaque analysis. The left panel shows AI-based plaque quantification with software from Cleerly Inc. allowing the evaluation of plaque progression over time. The right panel shows the Elucid Vascucap Software for structural and plaque component-based quantitative profiles of coronary plaque.

all ACS occurs in patients without significant (>50% diameter) stenosis.[15] These are most likely caused by abrupt disruption of vulnerable, highly inflamed non-obstructive atherosclerotic plaques. While HRP features can identify vulnerable plaques, the evaluation of cardiac adipose tissue could detect this inflammation and may be a potential early indicator of future or even ongoing high-risk plaque development.[6] Several adipose tissue biomarkers currently being investigated include epicardial adipose tissue (EAT) and PCAT volume and density. Obesity, diabetes, and other genetic and environmental factors can contribute to EAT hypertrophy which is associated with failure of triglyceride storage, increased lipolysis, and inflammation.[16] PCAT, in closer vicinity to the coronary arteries, is hypothesized to be a more specific bidirectional marker of coronary inflammation and therefore of the CAD status.[17] Quantitation of adipose biomarkers requires time-consuming manual analysis and is dependent on accurate segmentation. AI technology is being increasingly utilized to assess adipose tissue-based cardiac biomarkers. AI can assist in the segmentation and quantification of adipose tissue depots while greatly reducing the labour intensiveness. CNN are often used to segment the EAT/PCAT depots and subsequently calculate the volume and/or attenuation. Although studies have not used these techniques for PCAT, they have been extensively used for EAT assessment.[18]

Radiomics

Radiomics refers to a quantitative approach to extract large amounts of tissue characterization features from imaging data using advanced mathematical analysis. Features extracted are related to the spatial distribution of the signal and pixel interrelationships and do not have to have a direct relationship with a clinical feature. Radiomics can be used to assess tissue properties of multiple important cardiac structures that are mentioned above such as coronary plaques and adipose tissues. Radiomics not only plays a role in adipose tissue quantification but is also of interest for the analysis of all cardiac imaging datasets and can be used for risk stratification and prognostic modelling.[19] Because of its capabilities in analysing large datasets and enabling the detection of complex relationships, AI algorithms using radiomics data are an ideal way to create predictive models that leverage cardiac imaging.

There are studies using radiomics to identify EAT and PCAT-specific features and subsequently use AI for diagnostic or prognostic purposes. An example is the study performed by Oikonomou *et al.*[20] on PCAT quantification showing that an AI-powered fat radiomic profile identifies inflammatory differences and improves cardiac risk prediction.

Prediction and outcomes

Availability of an increasing number of cardiac risk imaging biomarkers offers a unique opportunity to develop predictive models that can add value to current risk scores and prognostic models. Current models utilize limited amounts of clinical risk factor data, but the addition of AI-assisted incorporation of imaging-based markers such as CAC scores, plaque morphology features, adipose tissue, and radiomics will likely provide more accurate and

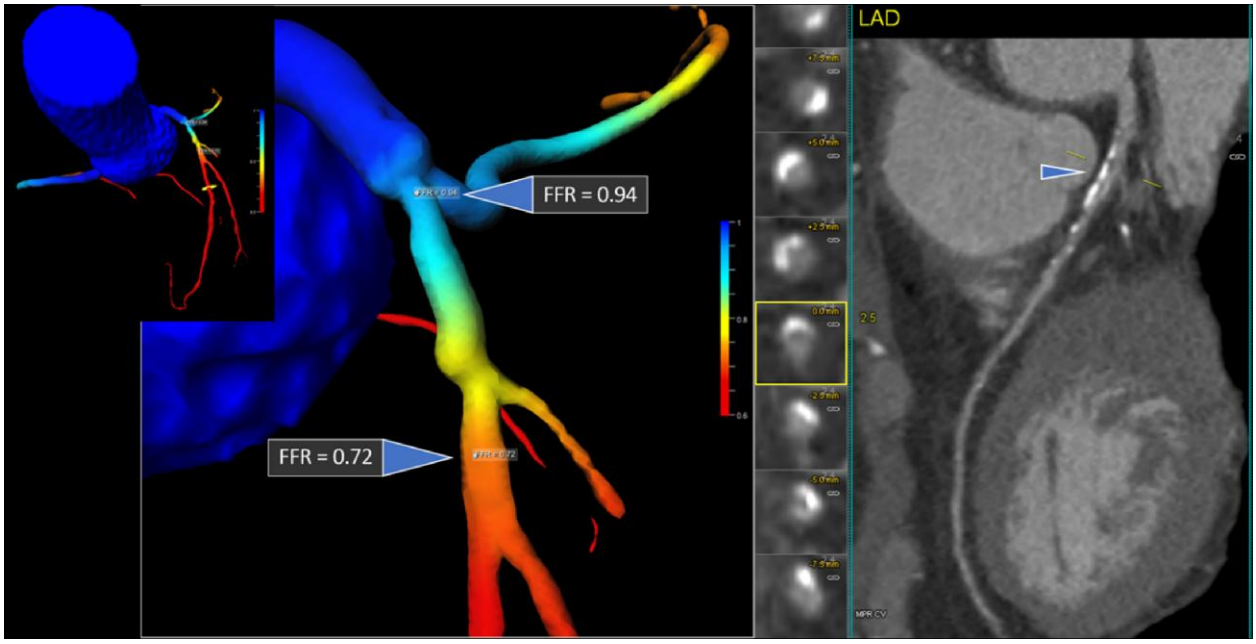

Figure 3 CT-FFR analysis on a patient with a severe stenosis in the proximal LAD (see CCTA, right panel). CT-FFR (left panel) shows functional significance with a CT-FFR drop to 0.72 (<0.75 is considered significant) using AI-based prototype from Siemens Healthineers (not intended for clinical use).

personalized models for risk assessment. However, its implementation into routine clinical workflow will require infrastructure that allows extraction of both clinical and imaging data and standardization of data formats.

Challenges

AI for CAD evaluation has some limitations. First is data accessibility, quality, and representativeness. Without large amounts of data that equally represent the target population, including accurate labelling and reference standards, AI will not be able to reach its full potential. Larger prospective studies are needed to reduce bias and prove the value of these parameters in representative populations. While one of the strengths of AI is to evaluate complex relationships in large amounts of data in an automated way, it also is sensitive to propagate bias in data and interpretation in an automated way. In addition, reproducibility needs to be proven, especially with the use of radiomics, as variability in ROI placements, etc. can affect reproducibility. External validation is needed to provide information on the accuracy of AI software in order to clinically implement the right algorithms and fulfil expectations. For AI solutions to have a beneficial impact on clinical workflow, data transparency, including fundamental functional principles, and reproducibility are essential. Clinicians need to build trust in the AI software in order to implement it into their daily practice. Currently, the clinical cost effectiveness and value of AI in practice is lacking and is a crucial step for reimbursement and for clinical implementation of AI-based software.

Summary

Artificial intelligence is set to change the medical sector and can greatly impact CAD evaluation. AI-based applications can play a significant role in the identification, quantification, and prognostication of CAD. Moreover, AI can play a significant role in the identification and clinical application of novel imaging biomarkers and workflow optimization for cardiac CT and coronary plaque analysis. AI can rapidly and accurately provide physicians with better data and information allowing better decision-making. We need to embrace and guide this technology to improve the quality of healthcare by improving patient treatment and outcomes.

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Data availability

No new data were generated or analysed in support of this research.

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