Machine Learning and Deep Neural Networks Applications in Computed Tomography for Coronary Artery Disease and Myocardial Perfusion

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Abstract: During the latest years, artificial intelligence, and especially machine learning (ML), have experienced a growth in popularity due to their versatility and potential in solving complex problems. In fact, ML allows the efficient handling of big volumes of data, allowing to tackle issues that were unfeasible before, especially with deep learning, which utilizes multilayered neural networks. Cardiac computed tomography (CT) is also experiencing a rise in examination numbers, and ML might help handle the increasing derived information. Moreover, cardiac CT presents some fields wherein ML may be pivotal, such as coronary calcium scoring, CT angiography, and perfusion. In particular, the main applications of ML involve image preprocessing and postprocessing, and the development of risk assessment models based on imaging findings. Concerning image preprocessing, ML can help improve image quality by optimizing acquisition protocols or removing artifacts that may hinder image analysis and interpretation. ML in image postprocessing might help perform automatic segmentations and shorten examination processing times, also providing tools for tissue characterization, especially concerning plaques. The development of risk assessment models from ML using data from cardiac CT could aid in the stratification of patients who undergo cardiac CT in different risk classes and better tailor their treatment to individual conditions. While ML is a powerful tool with great potential, applications in the field of cardiac CT are still expanding, and not yet routinely available in clinical practice due to the need for extensive validation. Nevertheless, ML is expected to have a big impact on cardiac CT in the near future.

Key Words: artificial Intelligence, computed tomography, coronary artery disease, machine learning, automated analysis

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In the last decades, computed tomography (CT) has become a mainstay in the evaluation of patients with coronary artery disease (CAD) and is recommended by several guidelines. According to the most recent guidelines from the European Society of Cardiology,[1] calcium scoring using CT bears a class IIb recommendation as a risk modifier for asymptomatic subjects, albeit not recommended to detect obstructive CAD. Moreover, CT angiography bears a class I recommendation for initial assessment of CAD in symptomatic patients, wherein CAD cannot be excluded by clinical assessment. In fact, CT angiography shows a high negative predictive value for excluding CAD and can thus be considered as a gatekeeper for invasive coronary angiography. More recently, new techniques that add functional analysis to anatomic imaging have been introduced. One of them is CT-derived fractional flow reserve (FFR), which allows estimation of residual vessel percentual blood flow after a stenosis through computational fluid dynamics models, that well reflects FFR values obtained at invasive coronary angiography. CT-derived FFR seems to provide incremental diagnostic value to CT angiography, potentially allowing the avoidance of invasive testing in some instances.[2] A second, promising technique is CT myocardial perfusion (CTP), which allows the assessment of the functional significance of stenotic lesions by assessing the wash-in and wash-out of contrast media in the myocardium. CTP can be performed at rest, like traditional CT angiography, but its main application, which allows the detection of inducible ischemia, is in stress CTP, which is performed during pharmacological stress. CTP can be static or dynamic, as regards whether the acquisition is performed at a single time point during the first-pass perfusion, or at multiple time points during the first-pass perfusion capturing the full signal intensity-time curves. Dynamic CTP has been proven to improve the diagnostic performance of CT angiography and yield a very high prognostic value for the occurrence of adverse cardiac events.[3,4] CTP was shown to add diagnostic accuracy to CT angiography along with CT-FFR, and prospective, multicenter studies that evaluate the impact of CTP on patient care are currently underway.[5,6] Myocardial perfusion can also be assessed from magnetic resonance imaging, which yields high accuracy for the detection of inducible ischemia. However, CTP may bear some advantages over magnetic resonance imaging such as the higher availability and lower cost, and the radiation dose related to such techniques, albeit non-null, is reasonably low.

Parallel to these advances in functional imaging, radiology has of late seen a steep rise in the use of artificial intelligence (AI), as reflected by a rapidly growing body of related literature. AI may be defined as the ability of a system
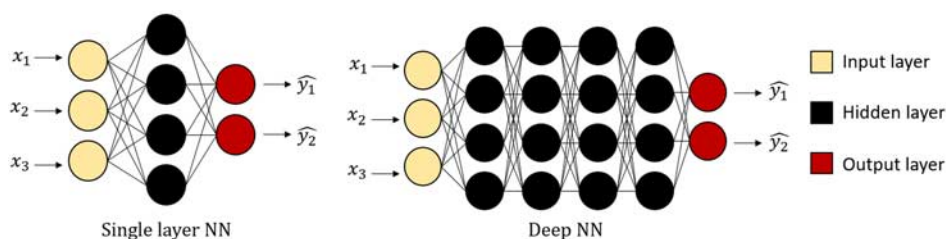
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FIGURE 1. Examples of a single-layer neural network (NN) used for machine learning, versus a 4-hidden layer deep NN.

to interpret data and to learn from it through adaptation, achieving the desired goals, allowing the analysis of large data sets in a short time, and the appraisal of complex patterns and relationships. This latter skill may provide AI an edge over human performance and be particularly relevant with the rise of big data.[7] Machine learning (ML) is a branch of AI in which models are built on the basis of training data sets that yield predictions for new, potentially large data sets without specific training. Deep learning represents a technique of ML that exploits artificial neural networks. These may be defined as deep neural networks (DNN) when multiple layers are utilized to predict an output from a given input. An example of a single-layer neural network versus a DNN is depicted in Figure 1.

With regard to cardiovascular imaging, AI may be particularly helpful in dealing with the optimization of image acquisition, in helping with image postprocessing that requires more and more time and skill as imaging tests become widely available and the number of analyzed features increases exponentially, and in developing new prognostic biomarkers for risk assessment. There is increasing literature on the potential and use of AI in cardiac CT. This work aims to outline some of the most recent ML-based innovations involving calcium scoring, CT angiography, and CTP. CT-FFR is another application in which AI plays an important role, but, in view of its complexity, this application will not be discussed here.

AI FOR CALCIUM SCORING

Coronary artery calcium (CAC) scoring is a CT screening tool for CAD, based on CAC that can be sensitively detected on noncontrast-enhanced cardiac scans. The amount of CAC is usually expressed as calcium volume, and as Agatston score.[8] The latter is used to guide the clinical management of patients, based on Agatston score categories that relate cardiovascular risk or percentile scores based on age and gender. The CAC score can be obtained by postprocessing of dedicated cardiac CT scans, by selecting calcium that lies in the coronary arteries and excluding other potential calcific areas such as bones or valvular calcifications (Fig. 2).

Concerning CAC, ML applications have been mostly focused on automatic detection and scoring, which may be particularly helpful in reducing postprocessing times, especially given that the demand for cardiac CT is rapidly increasing and CAC scoring may in the future be used for cardiovascular screening.[9] Among the first studies testing ML for fully automated CAC scoring is work by Wolterink et al.[10] They relied on the first identification of CAC based on intensity on noncontrast CT scans, and subsequent classification in coronary and noncoronary calcifications based on analysis of additional features such as size, shape, and location with a decision tree-based approach, followed by quantification. This method was tested on 1013 consecutive CT scans, and it reached a sensitivity of 0.87 for CAC lesions. There was a κ of 0.94 in assigning CAC-based risk categories compared with manual segmentation by a human observer, thus indicating strong agreement. A subsequent study by Wolterink et al[11] aimed to quantify CAC on CT angiography scans with the aid of paired convolutional neural networks, achieving a satisfactory sensitivity of 0.71 and 83% agreement in CAC-based risk classification compared with manual annotation by an expert human observer. Yang et al[12] aimed to automatically detect calcified lesions of the coronary arteries using automatic CTA vessel segmentations performed in contrast-enhanced scans and registering them for calcium detection on noncontrast
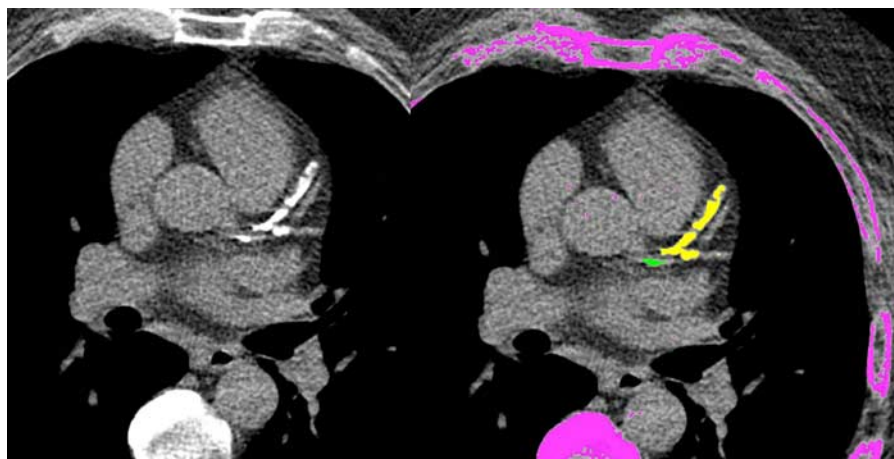

FIGURE 2. Automatic detection of calcium on unenhanced computed tomography scan of the heart.
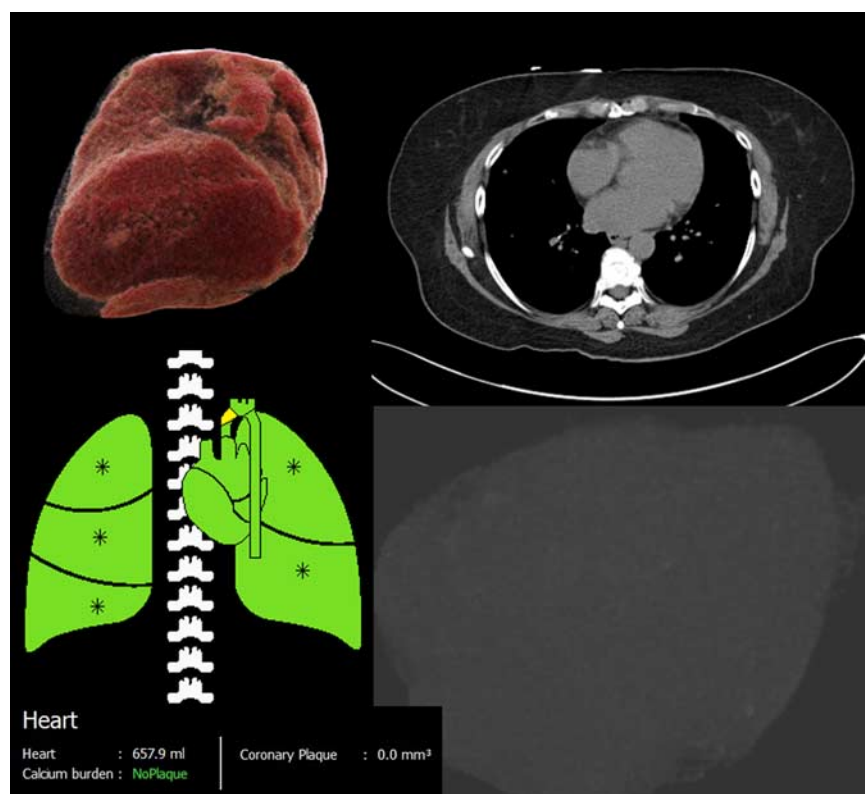
FIGURE 3. Output from Ai-Rad Companion in a subject with no coronary calcifications. *Lobes where lesions were detected.

scans. They achieved a high sensitivity of 0.94 compared with an experienced human observer on a data set of 40 CT examinations. A CAC segmentation method developed by Shahzad et al[13] was also tested on the same data set, yielding a slightly lower, albeit high, sensitivity of 0.85. Automatic CAC detection was also studied on low-dose, noncontrast CT scans acquired for lung cancer screening, which have been demonstrated to be reliable sources for CAC detection.[14] Lessman et al[15] achieved a κ of 0.91 for Agatston risk classification compared with an expert human observer. They used DNNs for automated CAC detection on 1687 nonenhanced, low-dose CT scans from the National Lung Screening Trial.[16] Another study by Cano-Espinosa et al[17] also utilized nongated, nonenhanced scans for Agatston score computation, reaching similar conclusions. On a database of 5973 scans, they used 4973 cases for training a 3D DNN and 1000 for testing, reaching a strong positive correlation ($r = 0.93$) with manual Agatston scoring. As regards CAC assessment on both contrast and noncontrast chest CT, Siemens (Siemens Healthineers, Erlangen, Germany) recently developed a preliminary application, AI-Rad Companion, which allows CAC quantification as absolute volume based on chest CT images. Examples of Ai-Rad Companion outputs in a healthy subject and in one patient with coronary calcifications may be seen in Figures 3 and 4. The performance of CAC assessment based on AI software in the clinical setting is yet to be established for large clinical samples.

AI has also been used to develop more comprehensive models involving CAC and other patient factors for the prediction of CAD. Namely, one study by Al'Aref et al[18]

utilized ML to build a model that yielded a good area under the curve (AUC) of 0.881 (95% confidence interval [CI], 0.869-0.895) in predicting obstructive CAD. Such a model was developed with a gradient-boosting ML algorithm for binary classification in obstructive CAD versus nonobstructive CAD on 13,054 included patients, split in a 3:1 ratio between training and validation sets. The model exploited calcium scoring combined with clinical variables such as age, sex, symptoms, and cardiovascular risk factors. Another study by Han et al[19] on 86,155 patients, combining 70 parameters including CAC, described a ML model for mortality risk assessment, which exhibited an AUC of 0.78 (95% CI, 0.66-0.90) on a validation cohort of 4915 patients.

Overall, automated Agatston score evaluation based on ML methods has reached good results. Risk prediction through ML adding CAC to other variables has been performed on vast samples; however, results still show a certain degree of room for improvement. In fact, while an AUC over 0.8 may indicate good performance, from a clinical perspective, it is ever important to not underestimate the probability of false negatives when ascertaining patients' risk, so that no patient may be undercared for. AI applications in image preprocessing for artifact reduction may be helpful in increasing postprocessing performance of CAC scoring, but, for this, there is still limited literature evidence. Future developments for AI in CAC are likely to include postprocessing applications with even higher agreement with human readers and thus viable for wide-scale clinical practice, possibly integrating preprocessing algorithms to enhance image quality.
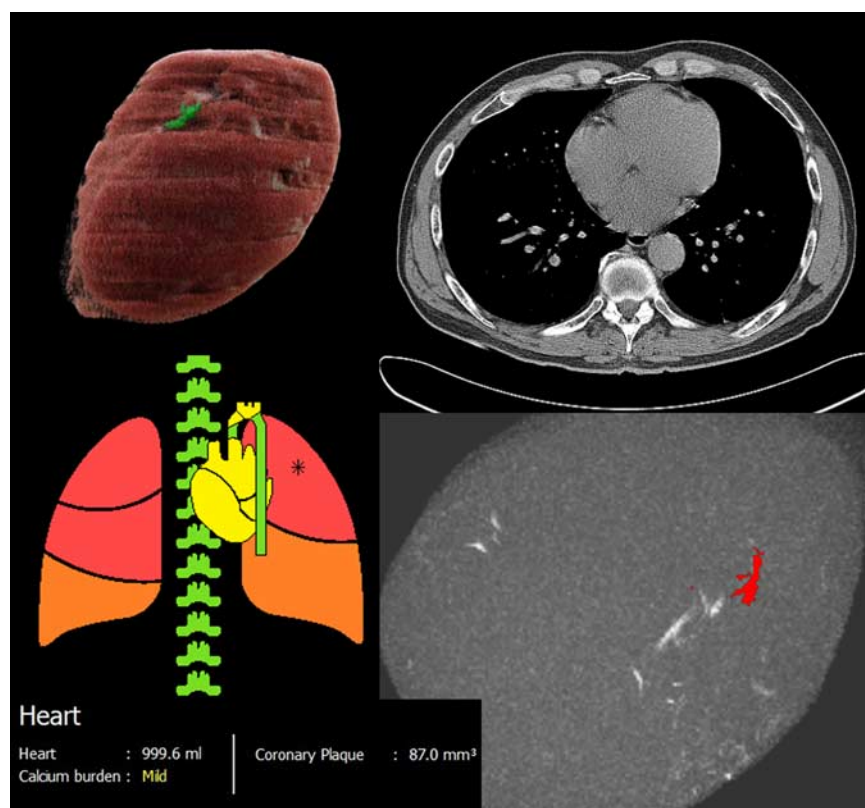
FIGURE 4. Output from Ai-Rad Companion in a patient with mild coronary calcifications. *Lobes where lesions were detected.

AI FOR CORONARY CT ANGIOGRAPHY

CT angiography is a key tool for the assessment of patients with chest pain, with a high negative predictive value for coronary stenoses that allows safe exclusion of epicardial CAD (Fig. 5), thus acting as the gatekeeper for invasive testing.[20] CT angiography allows for accurate anatomic delineation of stenotic lesions, and, to a certain extent, for functional evaluation with the aid of novel biomarkers such as FFR or CTP.[1] Moreover, CT angiography has been reported to add prognostic value, even in instances

FIGURE 5. Example of detection and dedicated depiction of the coronary arteries on a computed tomography coronary angiography scan.

when its use was labelled as "inappropriate."[21] ML calculations of FFR perhaps represent the most developed application in this fi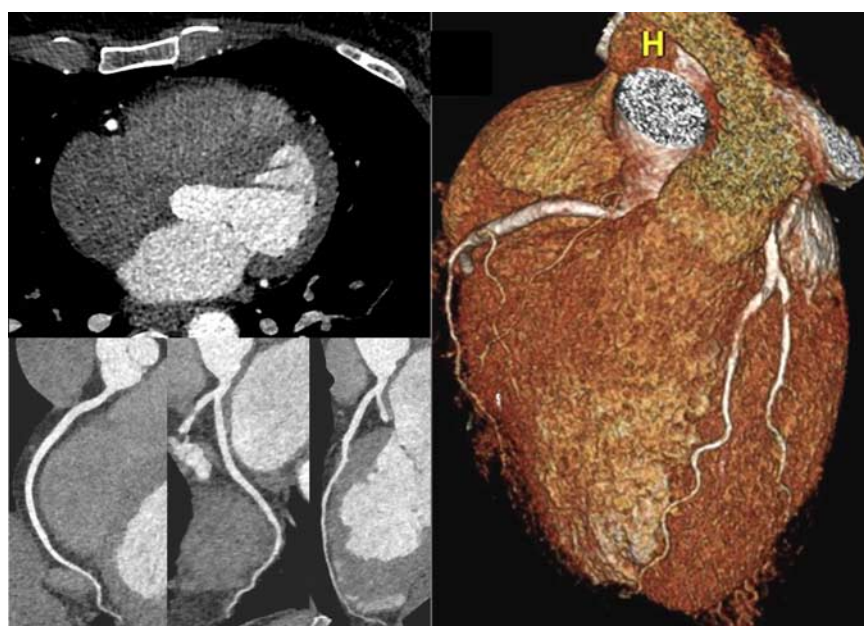eld, as ML has been shown to be a valid substitute of more cumbersome computational fluid dynamics approaches.[22] However, given its broadness and complexity, such a topic might probably benefit from a dedicated commentary. ML approaches in CT angiography involve applications related to image acquisition and image preprocessing, postprocessing, and risk prediction.

Concerning image acquisition and image preprocessing, different studies have used ML methods for optimization of protocols, as artifacts such as blooming subsequent to the presence of calcific plaques, and to a lesser extent with newer CT technology, and motion artifacts can occur in CT angiography. For instance, Tatsugami et al[23] proposed an ML algorithm involving a 10-layer DNN for image restoration, which was tested on 30 patients undergoing CT angiography. The application of this algorithm led to higher image score quality, assessed by an experienced human observer using a 4-point scale, compared with hybrid iterative reconstruction (2.96 vs. 3.58, respectively). Another study, by Lossau et al,[24] described an ML-based algorithm for motion estimation and correction in CT angiography, which was tested on 12 real-world clinical cases, outlining its feasibility and yielding better subjective image quality scores, as assigned by experienced researchers. Liang et al[25] described an additional motion correction algorithm, aimed for image quality improvement in patients with high heart rate (over 75 beats/min). Such an ML-based approach significantly improved image quality, from 2.81 to 3.56 on a 4-point scale, as evaluated by an experienced radiologist.

With regard to image postprocessing, one of the main goals of AI in CT angiography is automated coronary segmentation, along with automated delineation and quantification of coronary plaques and stenoses.[26] One potential endpoint of this effort to optimize patient management would be to obtain an automated CAD-Reporting and Data System (CAD-RADS) score, which is a standardized system for reporting results with regard to coronary stenoses in patients undergoing CT angiography, strongly related to clinical outcomes.[27] In this regard, among the first studies was one by Higgins et al[28] from 1996, which automatically extracted a model of arteries from CTA scans using a system based on the ANALYZE framework. Zhou et al,[29] in 2012, developed a method by extracting the coronary arterial tree from CTAs, which exhibited a miss rate of 25 coronary segments over 20 cases. In 2014, Zhou et al[30] achieved a sensitivity of 0.86 for the overlap between automatic and manual segmentation with an upgrade of the previously developed model. In a more recent work, by Ghanem et al,[31] a method of automated coronary wall detection was proposed. This included segmentation of atherosclerotic plaques, recording a dice similarity coefficient around 80%. Some commercially available software has attained good performance in automated coronary segmentation on CTA; however, performances on difficult cases, such as patients with coronary anomalies, stenoses, or calcifications, are still not completely satisfactory. This software does not use AI, and it might be possible that the introduction of ML might help overcome the issues that render automatic segmentation tricky in some instances. Among the difficulties that can hamper automated coronary segmentation, the image quality might be the most relevant, especially considering the small diameter of the coronary arteries. This may partially explain why fully automated coronary segmentation

has not yet reached optimal performances for more complex anatomies or extensive coronary atherosclerosis.

Another field where AI can prove useful in CTA is plaque analysis, as the different composition of coronary plaques might lead to different patient outcomes. On this subject, a study by van Assen et al[32] investigated an AI-based automated model for plaque analysis and characterization, which allowed prediction of adverse outcomes. This kind of model significantly increased the accuracy of adverse event prediction compared with the analysis of only clinical variables from 0.629 to 0.872. Zreik et al[33] proposed an ML-based, convolutional neural network approach for detecting and classifying coronary plaques and stenosis. The authors used coronary CT angiography scans from 81 patients for network training, and 17 for validation, and found an accuracy of 0.77 for plaque analysis and of 0.80 for stenosis analysis. The accuracy of AI-based analysis was not significantly different from the accuracy for human observers, which were 0.80 and 0.83, respectively. Zhao et al[34] proposed another automatic plaque detection and classification framework based on ML and feature analysis, yielding an accuracy of 0.94 compared with an experienced human observer on 18 CT angiography examinations.

With regard to risk assessment, some large cohort studies have been performed to predict outcomes based on patient characteristics such as risk factors and cardiac CT results. Among the most recent studies conducted on large cohorts is one by van Rosendael et al[35] who added plaque assessment to an ML approach for risk stratification. Their model analyzed 35 different CT angiography variables and was based on gradient-boosted decision trees. The data set of 8844 patients was divided in a 4:1 ratio between training and validation. The ML approach to risk stratification yielded a *c*-statistic of 0.771, significantly higher than *c*-statistics for non-ML approaches (ranging from 0.685 to 0.701). Motwani et al[36] developed and tested an ML model for predicting mortality utilizing features from CT angiography, on a population of 10,030 patients with suspected CAD. Of the cohort, 90% was used for training and 10% for testing. The AUC of their model was 0.79 (95% CI, 0.77-0.81), compared with the highest AUC obtained from traditional risk assessment of 0.64 (0.62-0.66).

CT angiography is most likely the field of cardiac CT, not including CT-FFR, where ML sees the widest available ranges of published studies and applications. However, some postprocessing applications, for instance plaque segmentation and quantification, have yet to reach good performance due to the associated intrinsic difficulties. Another important issue weighing on the task of coronary segmentation is the lack of big, labelled data sets, also derived from the fact that manual coronary labelling is a highly time-consuming task. Considering this perspective, future developments might include the creation of additional open-access data sets labelled by experts that would allow the training and testing of novel ML algorithms on reliable sources. The prognostic value of ML in CT angiography shows promising results with regard to the prediction of adverse outcomes. This may be especially interesting, as studies in this field were conducted on large samples, thus potentially providing additional value to the currently available models (Table 1).

AI IN CTP

Given the relative novelty of CTP, so far, only a few studies have developed related AI applications. An example of

TABLE 1. Main Applications of Machine Learning in Cardiac CT, Divided in Fields According to CAC, CT Angiography, or CTP

	Calcium Scoring	Computed Tomography Angiography	Computed Tomography Perfusion
Image preprocessing		Image quality improvement: image restoration,[23] motion estimation and correction,[24] adjustment for heart rate[25]	
Image postprocessing	Automatic quantification on noncontrast CT: high concordance with Agatston scores assigned by an experienced reader ($\kappa = 0.94$[10])	Coronary segmentation: DSC 0.80[31] including coronary wall and plaque contouring	Segmentation of CTP images: AUC of 0.73[37] compared with an experienced reader
	Automatic quantification on contrast-enhanced CT: high sensitivity in detecting calcifications compared with an experienced reader (sensitivity 0.94[12])	Plaque detection and characterization: predicting outcomes subsequent to automatic plaque characteristics with an accuracy of 0.872,[32] and accuracy of 0.94[34] for plaque detection and classification	Rest CTP assessment: AUC of 0.75[38] for functionally significant stenosis
	Automatic quantification on nongated CT: high concordance with Agatston scores assigned by an experienced reader ($\kappa = 0.91$[15])		
Risk assessment	Risk of obstructive CAD: AUC of 0.881[18] including CAC and clinical data	Risk of major cardiac events: AUC of 0.79[36] combining CT angiography features and clinical data	
	Risk of mortality: AUC of 0.78 including CAC and clinical data[19]		

The most recent studies or the ones yielding the best performances for each specific application are briefly outlined.
DCS indicates dice similarity coefficient.

myocardial CTP image postprocessing is depicted in Figure 6. Concerning image postprocessing, Xiong et al[37] compared 3 different ML approaches with the segmentation of CTP images, which they tested on 140 cases. They found that one of them, AdaBoost, performed better than the other 2, with an AUC of 0.73, compared with manual segmentation by an experienced observer. On the same topic, Han et al[38] proposed a supervised ML algorithm based on a gradient-boosting classifier for resting CTP analysis. This algorithm was tested on 252 patients with suspected CAD. The study showed that adding resting CTP to the assessment of patients with CT angiography brought a significant increase in diagnostic AUC for functionally significant stenosis from 0.68 (95% CI, 0.62-0.74) to 0.75 (95% CI, 0.69-0.81).

Among the potential future uses of ML in CTP, automatic segmentation of the myocardium with automatic assessment of perfusion defects on both static and dynamic data sets might be particularly beneficial, to reduce human postprocessing times in view of the growing numbers of CTP examinations performed.[39] Moreover, including CTP data in risk assessment ML models may potentially lead to a further increase in prognostic accuracy, as multivariate analyses previously showed promise in this regard.[3]

CONCLUSIONS

While CT for the assessment of CAD has not been the main field of application of ML techniques in radiology, recent studies show promising findings that suggest a growth toward wider investigation and application of such techniques for thoracic and cardiovascular CT.[40] The largest samples in the field of ML with the inclusion of cardiac CT
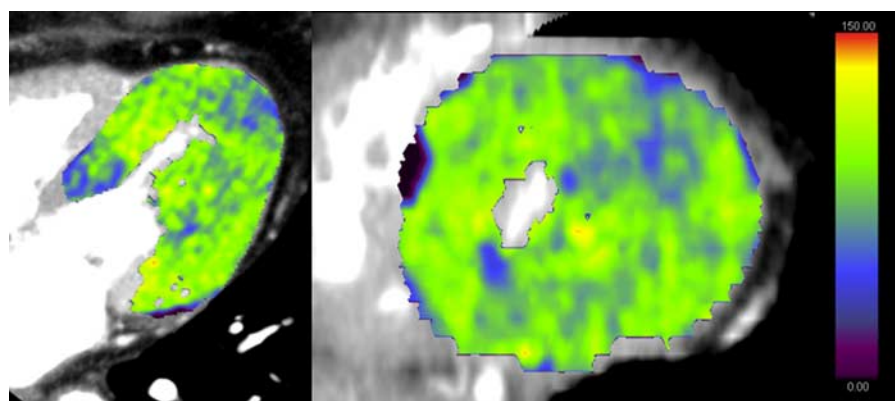

FIGURE 6. Example of myocardial computed tomography perfusion postprocessing analysis, depicting areas with different degrees of perfusion in different colors, as reported in the colormap on the right.

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have focused on CAD prediction. The number of studies that focus on cardiac CT preprocessing and postprocessing is more extensive, but sample sizes in CAD CT image preprocessing and postprocessing studies using AI are still limited. The reason for this may be heterogeneity in image acquisition, and difficulties related to the lack of availability of large data sets labelled by experts. While, so far, only a few ML applications are available for routine use in clinical cardiac CT practice due to the need of extensive validation, this is projected to change soon. New AI solutions are currently becoming clinically available such as the AI-Rad Companion for chest CT applications. One of the first AI-based cardiac CT solutions that seem close to clinical implementation is automated CAC scoring. New applications or models are expected to be of potential benefit for all aspects involving CAD assessment on cardiac CT.

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