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A Review on the Estimation of Coronary Fractional Flow Reserve Using Artificial Intelligence

Koroner Fraksiyonel Akım Rezervinin Yapay Zeka Kullanılarak Tahmin Edilmesi Üzerine Bir İnceleme

ABSTRACT

Coronary artery disease (CAD) is the leading cause of death worldwide. The most widely used and precise method for diagnosing CAD is invasive coronary angiography (ICA). Fractional flow reserve (FFR) is an index of the functional severity of coronary stenoses that requires additional invasive intervention during ICA. With advancements in artificial intelligence (AI) technology, the estimation of FFR using AI is gaining popularity to meet the need for fast, accurate, and less invasive FFR estimation that can integrate into physicians' workflows. This review presents the current progress in this area by analyzing studies employing various approaches.

Keywords: Angiography, artificial intelligence, coronary artery disease, fractional flow reserve

ÖZET

Koroner Arter Hastalığı (KAH) dünya çapında en yaygın ölüm nedenidir. KAH tanısı için en yaygın kullanılan ve kesin yöntem invaziv koroner anjiyografidir (İKA). Fraksiyonel akım rezervi (FAR), İKA sırasında ayrıca invaziv girişim gerektiren koroner stenozların fonksiyonel ciddiyetinin bir indeksidir. Yapay zeka (YZ) teknolojisindeki ilerlemelerle birlikte, hekimin iş akışına entegre edebilecek hızlı, doğru ve daha az invaziv FAR değerlendirmesi ihtiyacını karşılamak için YZ kullanılarak FAR tahmini popülerlik kazanmaktadır. Bu alandaki mevcut ilerleme, çeşitli yaklaşımları kullanan çalışmalar incelenerek ortaya konmuştur.

Anahtar Kelimeler: Anjiografi, yapay zeka, koroner arter hastalığı, fraksiyonel akım rezervi

REVIEW
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Coronary artery disease (CAD) is a type of heart disease in which the coronary arteries (CAs), the arteries of the heart, are unable to deliver sufficient oxygen-rich blood to the heart due to stenosis.[1] It is the leading cause of death worldwide, accounting for 8.9 million deaths in 2019.[2] Diseases of the circulatory system are also the leading cause of death in Türkiye, representing 35.4% of all deaths, with CAD being the most prevalent among these at 42.3% in 2022.[3]

There are both invasive and non-invasive tools for assessing coronary blood circulation and diagnosing CAD. Non-invasive tools include electrocardiography, echocardiography, stress testing, computed tomography, and cardiac magnetic resonance imaging (MRI), which are easier to perform and have fewer complications. Invasive tools include intravascular imaging modalities and invasive coronary angiography (ICA), both of which require inserting instruments into the body.[4] The choice of diagnostic procedure depends on the severity of the patient's symptoms. The most commonly used invasive diagnostic tool is ICA. During this procedure, an interventional cardiologist inserts a catheter through the large arteries of the body up to the aorta until its tip reaches one of the two CAs. A radio-opaque contrast agent is then injected through the catheter, and a series of X-ray images are captured. The coronary arteries and capillaries become visible for a few seconds on X-ray before the contrast agent is washed away. Coronary angiography data consist of sequences of black-and-white images. Since a series of images are captured every second, they are often viewed as videos. In every angiography video, there is a frame called the "key frame," in which the contrast agent has dispersed, making all the coronary vessels visible. Interventional cardiologists examine the angiography video to assess lesions, plaques, bifurcations, and stenoses of the CAs. Immediate diagnostic angiography is recommended for patients presenting with acute coronary syndrome. Depending on the significance of ICA findings, invasive management may be performed in the same session.[4] By visual inspection of the angiography, mild and severe stenoses, as well as coronary artery occlusions below 50% and above 70%, are easier to diagnose, whereas intermediate stenoses (50% to 70%) are more difficult to assess. Expert evaluations rely on experience and clinical judgement, leading to potential disagreements among specialists.[5]

Fractional Flow Reserve (FFR), an invasively determined index of the functional severity of coronary stenoses, is defined as the ratio of the pressure distal (after) to a stenosis to the pressure proximal (before) to the stenosis.[6] To determine FFR, a wire with a pressure-sensitive tip is inserted through the angiography catheter to measure pre- and post-stenosis pressures. The FFR pressure sensor is calibrated to "1" at the aorta. FFR was first introduced in 1993 by Pijls et al.[7] as a tool to assess the functional severity of stenosis. The DEFER study[6] (Deferral of Percutaneous Coronary Intervention) and its five-year follow-up[8] demonstrated that patients with FFR values greater than 0.75 had a risk of cardiac death or myocardial infarction related to the stenosis lower than 1% per year, with no additional benefit from stenting. In the FAME study[9] (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) and its follow-up FAME 2 study,[10] FFR-guided percutaneous coronary intervention (PCI), which involves placing a stent along the stenosis, combined with the best available medical therapy, was compared with the best available medical therapy alone. The study demonstrated that in patients with stable coronary artery disease and functionally significant stenoses, FFR-guided PCI reduced the need for urgent revascularization. As a result of these and other studies, the FFR index has become a unique marker for identifying ischemia-prone lesions in patients with coronary artery disease.[11,12] Further research established 0.80 as a more precise cut-off value,[9] with FFR values between 0.75 and 0.80 considered the "gray zone."[11] Despite its recommendation as a standard diagnostic tool in the European Society of Cardiology guidelines,[13] FFR is not widely used due to limited availability, high costs, technical complexity, and insufficiently trained personnel.[12] Additionally, vasodilator drugs, which are administered during FFR measurement to maintain maximum blood flow in the CAs, may have side effects that further limit its use.

Artificial intelligence (AI) is a branch of computer science that focuses on developing machine or software-based intelligence. AI-based solutions are widely applied across various fields, including science, industry, the internet, and medicine. One of the key techniques used to solve AI problems is Artificial Neural Networks (ANNs). ANNs consist of tens to millions of artificial neurons, where each neuron functions based on its inputs, using assigned weights to each input. With advancements in AI technology, several applications have been developed in recent years in the medical field, making healthcare more accurate and efficient. Current AI applications in cardiovascular care include the analysis of electrocardiograms, coronary computed tomography angiography, transthoracic echocardiography, coronary angiography, chest radiographs, medical notes, MRI, intravascular ultrasound, intravascular optical coherence imaging, and photoplethysmography.[14,15] The aim of this review is to provide an overview of the use of AI in FFR estimation.

ABBREVIATIONS

ANNs	Artificial Neural Networks
CAD	Coronary artery disease
CAs	Coronary arteries
CCTA	Cardiac computed tomography angiography
CFD	Computational flow dynamics
CT-QFR	CCTA-derived quantitative flow ratio
FFR	Fractional flow reserve
FFRCFD	CFD-based non-invasive FFR
FFRD	Diameter flow method-based FFR
FFRU	Novel method-based FFR
ICA	Invasive coronary angiography
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography

Materials and Methods

We searched PubMed, Google Scholar, and the Institute of Electrical and Electronics Engineers Xplore up to January 2024 for original articles related to the use of AI in FFR prediction. The following search terms, including synonyms and abbreviations, were used: "coronary angiography AND fractional flow reserve AND artificial intelligence OR machine learning OR neural network." Duplicate records were removed. The identified articles are summarized in Appendix 1, and the methods used to predict FFR values are outlined in Figure 1.

Commercial Software Predicting FFR Without AI

There are commercial non-invasive techniques that utilize computational flow dynamics (CFD) on coronary angiograms to predict FFR. However, these techniques have specific requirements, such as multiple imaging angles, certain image quality standards, high costs, and long calculation times, often taking several hundred seconds.[16-18] A recent study suggests that the presence of an FFR pressure wire within a cardiac catheter can adversely affect FFR measurements, a factor not accounted for in existing CFD-based non-invasive FFR (FFR_{CFD}) technologies.[19] Several major companies offer FFR_{CFD} prediction software. However, its overall accuracy has been found to be low in the gray zone (0.75 to 0.80), often necessitating follow-up with invasive FFR in clinical practice.[18,20] Fearon et al.[21] used a commercial software solution that reconstructs a 3D representation of the coronary tree using multiple-angle angiograms and estimates flow based on calculated vessel volume. This non-AI approach, which employs CFD, is slow and cumbersome. Zhang et al.[22] used commercial software to construct a 3D reconstruction of the CAs using cardiac computed tomography angiography (CCTA) images. Different commercial software solutions were utilized to remove noise, smooth the images, calculate the diameter and length of the vessel, and load boundary conditions for pressure or mass flow. Finally, the reconstructed CA was imported into another commercial software program for CFD simulation. CCTA-derived FFR (FFR_{CT}), quantitative coronary angiography (QCA), a software-based technique that quantifies coronary stenosis by comparing the diameter of the stenosis with a reference diameter, diameter flow method-based FFR (FFR_D), and a novel method-based FFR (FFR_U) were all calculated and compared with invasive FFR, demonstrating the superiority of FFR_U. CCTA-derived quantitative flow ratio (CT-QFR)

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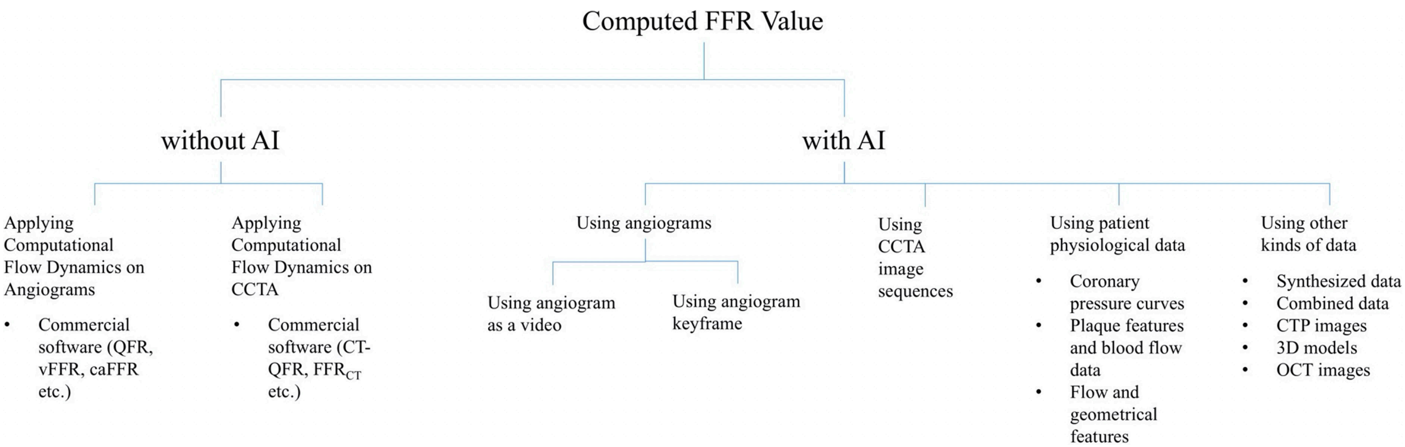

Figure 1. Methods to predict fractional flow reserve.

is an on-site, non-invasive technique for estimating invasive FFR. Dahl et al.[23] compared CT-QFR with FFR and found that CT-QFR remains inferior to FFR, regardless of whether it is measured lesion-specific or at the most distal point of the lesion. However, a lesion-specific CT-QFR approach demonstrated superior discrimination of hemodynamically obstructive CAD compared to a most distal CT-QFR approach. Lesion specific CT-QFR identified most cases of hemodynamically obstructive CAD, while a normal CT-QFR excluded hemodynamically obstructive CAD in the majority of patients.

Commercial Software Using AI

Several approaches exist for estimating FFR using AI, and commercial AI-based software is already available. Roguin et al.[24] used an ANN to calculate FFR values from multiple-angle angiograms directly from the angiography machine in 37 seconds. Although they reported a 90% accuracy level for predicting whether an FFR value was lower or higher than 0.8, their dataset consisted of only 31 patients, which is insufficient to draw definitive conclusions. Griffin et al.[25] used CCTA images to train an AI model and compared the results with laboratory-interpreted QCA and measured FFR. The commercial software employed convolutional network models VGG-19 and 3D U-Net). Laboratory-interpreted QCA was used as the ground truth. While the AI model performed similarly to QCA, both were inferior to FFR in terms of sensitivity.

AI Applied to Patient Physiological Data

A common approach is to gather data on the patient's physiological characteristics. This approach is also used in combination with image or video processing. Zimmermann et al.[26] utilized resting aortic and distal coronary pressure curve data, trained models using Convolutional Neural Network (CNN) and Recurrent Neural Networks (RNN), to predict FFR values. They found the diagnostic accuracy to be 77-79%. They concluded that resting pressures alone are insufficient and that hyperemia induction should remain the standard practice for FFR prediction. Lin et al.[27] utilized CCTA-based quantitative plaque features and PET/CT-based (positron emission tomography/computed tomography) myocardial blood flow data to train an XGBoost network and compared the results with FFR$_{CT}$ derived from CCTA. Plaque quantification was performed by an independent laboratory, and FFR$_{CT}$ was derived using dedicated commercial software. While the results aligned with FFR$_{CT}$, they remained inferior to invasive FFR. Lee et al.[20] used morphological features, such as flow and geometrical characteristics extracted from CCTA, to train two neural networks and six machine learning (ML) algorithms, comparing the results with measured FFR values. CCTA images were processed to extract morphological features of the coronary arteries, and synthetic vessel models were generated based on patient data to increase data volume. The multi-layer perceptron model achieved the highest gray zone accuracy of 98.9%, but its overall accuracy was only 44.1%. The models were tuned specifically for optimal performance in the gray zone, with the highest accuracy reaching 67.6%.

AI Applied to CCTA Images

Another approach is to process non-invasive CCTA images. Candemir et al.[28] used CCTA images to train a 3D-CNN to detect stenoses and compared the results with expert reviews. First, a centerline extraction method was applied to CCTA sequences to locate the coronary arteries and their branches within the CCTA image datasets. A straightened longitudinal view of the vessel was obtained, followed by clamping and length equalization. The processed data were then applied to a 3D-CNN architecture. While the average classification accuracy was 90.9%, the positive predictive value was 58.8%. The prepared vessel views could potentially be used for flow rate detection, though this was not explicitly mentioned. Fossan et al.[17] used CCTA images to train a Feedforward Neural Network (FFNN) and compared the results with measured FFR values. A hybrid approach was proposed, where vessel segmentation, 3D modeling, and 3D flow calculations were performed using commercial software. The dataset was limited to 90 patients; however, the neural network outperformed the CFD model. Additionally, the purely data-driven FFNN performed better than the combined physics-informed FFNN. The neural networks exhibited a positive bias, predicting higher FFR values, whereas the CFD model showed a negative bias.

AI Applied to ICA Key Frames

A third approach is to process the angiography key frame or a portion of it that captures the lesion and its surroundings. However, using a single image has limitations, as coronary vessels are 3D structures, and stenoses can be eccentric, sometimes requiring multiple projections for a physiological analysis. Selecting a single frame from multiple ICA frames may lead to a loss of information. Zhou et al.[29] used ICA video key frames of the right coronary artery obtained from right anterior oblique and left anterior oblique projections. They employed ResNet18 for key frame extraction and U-Net for vessel segmentation. The results were compared with expert reviews. Stenosis size was measured by counting pixels on the key frame, a method similar to expert manual assessment. Cho et al.[30] measured angiographic lumen diameters, computed 24 angiographic parameters based on diameter plots, and incorporated four clinical features to form a dataset. They trained an XGBoost algorithm and compared the results with measured FFR values. Angiographic lumen segmentation on key frames was performed using commercial edge detection software. Erroneous segments were manually corrected, increasing processing time and reducing automation. The angiography-based ML model predicted FFR ≤ 0.80 with a sensitivity of 84%, specificity of 80%, and an overall accuracy of 82%. Although not directly related to FFR estimation, the endpoints align with the intent of the FFR procedure. Mahendiran et al.[31] used ICA image patches to train a ResNet18 algorithm. They compared the results with expert reviews, commercially derived quantitative flow rates, and stenosis parameters against actual patient conditions. Using two angiographic views, they attempted to estimate future culprit lesions. Feature engineering was required to prepare the image patches. The deep learning (DL) algorithm achieved an accuracy of 0.78, whereas expert review, stenosis diameter, stenosis area, and quantitative flow rate had accuracies of 0.58, 0.58, 0.60, and 0.70, respectively. These results indicate that DL outperforms other approaches in predicting future culprit lesions.

AI Applied to ICA Videos

The final approach involves processing angiography videos directly or after preprocessing. Zhao et al.[32] used ICA videos to train a CNN for vessel segmentation and compared the results with manually calculated coronary flow reserve (CFR). Two loops of the same angiographic projection, one taken at rest and one during hyperemia, were used to calculate CFR. CFR differs from FFR as it is defined as the hyperemia-to-rest flow ratio and is used to assess microvascular dysfunction. Patients with an FFR > 0.8 but low CFR have a worse prognosis. FFR and CFR disagree in approximately 32% of cases. Vessel length is calculated, and a length/time curve is derived using frame count. Flow velocity is determined by fitting a straight line to the length/time curve. CFR is calculated by dividing hyperemic flow velocity by resting flow velocity. The same method is applied in a laboratory to calculate CFR_{manual}. The automatically calculated CFR_{auto} showed moderate agreement with CFR_{manual}. However, manual calculation of CFR is not feasible.

AI Applied to Other Types of Data

Carson et al.[33] generated virtual single- and multi-vessel networks, trained multivariate polynomial regression (MPR), FFNN, and long short-term memory models on synthesized data, and compared the results with data from 25 real patients. The diagnostic accuracy of the 1D single-vessel model was 72% when tested with real-world data. The primary limitation of the study was the absence of sufficient real-world data. Sun et al.[34] generated 3,028 idealized stenosis models to train a Back Propagation Neural Network (BPNN) and attempted to predict stenosis resistance. They tested the network using FFR data from 30 patients. Stenosis resistance is a key parameter in calculating FFR_{CT}. FFR_{CT} was calculated using 3D CFD simulations of artery models reconstructed from CCTA images of the patients. BPNN-based FFR_{CT} and CFD-based FFR_{CT} were compared. The FFR_{CT} derived from BPNN-predicted stenosis resistance demonstrated an excellent accuracy rate compared with clinically measured FFR. However, due to CFD analysis, blood and vessels were assumed to be idealized. Muscogiuri et al.[35] used computed tomography perfusion (CTP) images to train a CNN and compared CCTA, CTP, and a combination of CCTA and CTP with measured FFR values. Image preprocessing was performed manually to reduce computational burden. The study found that CTP significantly improved the detection of hemodynamically significant CAD compared to CCTA alone. The best sensitivity and specificity, compared to invasive FFR, were 93% and 83%, respectively. Xue et al.[36] created a 3D hybrid model using ICA key frames and a 2D CCTA model, employing 13,000 synthetic and 180 real coronary trees to train a multilayer perceptron network and a bidirectional RNN. The results were compared with measured FFR values. The hybrid model was constructed using the overall spatial structure from the CCTA centerline combined with ICA-derived vessel radii. The test dataset was small, consisting of 67 vessels from 40 patients. Sensitivity was 100% for all types of vessels and vessel segments, but specificity varied between 71.43% and 94.44%. Statistically, the dataset was insufficient to draw definitive conclusions. Farajtabar et al.[37] used geometrical features of the artery and velocity boundary conditions to train a FFNN. These features were obtained through CFD simulations on synthetically generated vessels. Given the features for each artery in the arterial network, the FFNN predicted pressure and velocity values at specific points within the artery network. Since pressure values at any point could be predicted, FFR could be easily calculated. The results were tested on three real coronary artery geometries and were found to be highly accurate. However, collecting features for each artery is a time-consuming task, and the use of only three real cases is insufficient to reach a definitive conclusion. Cha et al.[38] used features obtained from optical coherence tomography (OCT) to train a Random Forest algorithm with additional features and compared the results with measured FFR values. The dataset consisted of 356 individual lesions in 130 patients. Seven features with varying weights were selected from OCT image analysis, including percent area stenosis, minimal lumen area, target vessel, distal lumen area, lesion length, plaque area, and proximal lumen area. The sensitivity, specificity, and accuracy of the OCT-based ML-FFR were 98.3%, 61.5%, and 91.7%, respectively. However, OCT is not a commonly available device in hospitals, and the need for feature engineering slows down the process.

Discussion

FFR measurement is a method introduced based on ICA with proven effectiveness in the treatment and diagnosis of CAD. Currently, FFR estimation is attempted using non-invasive methods, both with and without AI. However, ICA remains superior as it allows for treatment within the same session and provides more comprehensive information than non-invasive methods.[39] The main limitations of FFR estimation methods other than ICA are as follows: Physiological data-based studies extract features related to patient physiology from imaging, diagnostic tools, and clinical data. However, feature extraction requires expertise and slows the process. The most commonly used non-invasive procedure, CCTA, is recommended for low-to-medium risk patients. However, CCTA lacks the temporal information that ICA provides, and achieving high-quality images requires the patient's heart rate to be low. The use of CCTA may be limited in patients with tachycardia, established CAD, prior stents, or extensive coronary calcification.[4]

The number of studies estimating FFR using ICA is limited. Studies focusing on angiography key frames discard flow information, which is a crucial factor in expert decision-making. Since some parts of the image do not show vessels or stenoses, the image must be preprocessed, either automatically or manually, to isolate relevant areas. Restricting the view to a single angle is not compatible with the 3D nature of CAs. On the other hand, processing angiography output as a video requires significant computing power. Newer angiography machines have imaging precision down to 0.1 mm, and a single video from one angle can be up to 100 megabytes. Naturally, collecting angiography data is difficult. For prospective studies, obtaining ethics committee approval is difficult, and working with physicians is demanding due to the daily operations of hospitals. Patients must sign informed consent forms, and physicians must adhere to an established workflow. For retrospective studies, gathering data from hospital databases is challenging, primarily because different physicians take medical notes in varying formats, and angiography databases are not seamlessly integrated into hospital databases. Additionally, there are variations in angiography device output resolutions and image quality. Physicians may have different opinions regarding angiography angles, vessels, and lesions, and each has their own interpretation style. Multicenter studies often take years to complete. To our knowledge, as of May 2024, there are no publicly available video angiography datasets with FFR values attached. Most studies in this field are not based on large datasets. Large multicenter datasets are primarily found in commercial software evaluations. The FFR estimation problem can be approached as a classification problem when determining whether FFR > 0.8. However, if the goal is to predict a specific FFR value, the problem becomes a regression problem.

Angiography images are X-ray-based, meaning that tissues, organs, blood, and bones appear in the background. Some patients have surgical stitches, stents, or implants that are visible in angiography. Additionally, multiple lesions on the same vessel or different vessels within the same image must be accounted for. Each patient has unique cardiac characteristics, as vessel size and shape vary. Some patients have congenital heart defects, which alter blood flow characteristics. These variations can compromise data quality and render it unusable.

On the other hand, some invasive and non-invasive diagnostic tools, such as OCT, cardiac MRI, intravascular imaging, CTP, and even FFR measurement systems are not available in every center. As a result, the number of studies based on these methods is limited.

AI methods for analyzing data are not standardized, which can introduce bias into studies. Typically, training and test sets are randomly selected, and study operators remain blinded to minimize bias.

Our study has some limitations. First, this review focuses on a highly specific topic within a rapidly evolving and dynamic field. Additionally, AI applications and methodologies vary significantly between studies, making it difficult to draw definitive conclusions. Furthermore, the time lag between writing and publishing the article can delay the dissemination of the latest research findings.

Conclusion

FFR is a powerful metric for evaluating CAD. Research continues to explore ways to gain more insights with fewer procedures. Estimating FFR without performing an actual FFR procedure would benefit both patients and physicians. Even though studies have attempted to estimate FFR through non-invasive or minimally invasive methods, the results remain unsatisfactory. Given its frequent and urgent use, along with the concurrent advantage of enabling treatment, incorporating FFR estimation into ICA appears to be a useful approach. Further studies are needed on this subject.

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Appendix 1. Coronary Fractional Flow Reserve Estimation Using Artificial Intelligence Studies

Authors	Dataset	Ground Truth	Input	Output	Method	Computation Time	Results
Fearon et al. 2019[21]	319 vessels from 301 subjects	Measured FFR value	10 fps ICA video with two or more projections with a minimum separation of 30°	Calculated FFR value	3D reconstruction of the coronary tree. Normal maximal flow is estimated based on the volume of coronary vessels and total coronary length.	Average processing time of 2.7 minutes (not including manual correction and lesion identification)	FFR measured from the coronary angiogram alone has high sensitivity, specificity, and accuracy compared with pressure wire-derived FFR.
Zhang et al. 2023[22]	86 vessels in 73 patients	Measured FFR value	CCTA images	Calculated FFR value	Diameter and length of the vessel are determined based on a 3D model and simulated for hemodynamics using CFD.	5 minutes per simulation	The proposed method can accurately and rapidly identify coronary blood flow, significantly improving the accuracy of FFRCT calculation.
Roguin et al. 2020[24]	31 patients	Measured FFR value	ICA video (three projections for the LCS, two projections for the RCA)	Calculated FFR value	ANN	37 seconds (attached to the angiography machine and used during angiography)	Positive predictive value 94%, negative predictive value 87%, accuracy 90%. Good accuracy in predicting positive or negative FFR.
Griffin et al. 2023[25]	1,007,945 images of 23,068 vessels from 3,671 patients for training and testing; 303 patients analyzed	Commercial QCA and measured FFR values	CCTA images with two orthogonal views for QCA	Calculated FFR value	VGG-19, 3D U-Net	10.3 ± 2.7 minutes	High diagnostic performance of AI-based evaluation for severe stenoses at both the 50% and 70% levels, with high correlation to QCA.
Zimmermann et al. 2021[26]	A total of 1,666 patients with 1,718 coronary lesions and 2,928 coronary pressure tracings were included	smFFR calculated by algorithm	Resting coronary pressure curves	FFR+ or FFR- < 0.8 or > 0.8	CNN, LSTM, GRU	Not applicable	Study achieved approximately 80% accuracy in predicting FFR, consistent with previously reported NHPRs.
Lin et al. 2022[27]	484 vessels from the NXT trial for training,581 vessels from the PACIFIC trial for evaluation	CCTA-derived FFRCT	CCTA-based quantitative plaque features	Score value	XGBoost	25 minutes per patient	An externally validated ML score integrating CCTA-based quantitative plaque features accurately predicts ischemia by invasive FFR.
Lee et al. 2022[20]	144 patients with intermediate stenosis on the LAD and 200 synthetic vessel models	Measured FFR value	Morphological features extracted from CCTA	Calculated FFR value	ANN, MLP, K-Nearest Neighbor, Random Forest, Gradient Boost, AdaBoost, Gaussian Process, SVM	Not applicable due to required feature engineering	Random forest model showed the highest performance before optimization. ANN model had the lowest MAE, and MLP had the highest gray zone accuracy after optimization.

Appendix 1 (cont). Coronary Fractional Flow Reserve Estimation Using Artificial Intelligence Studies

Authors	Dataset	Ground Truth	Input	Output	Method	Computation Time	Results
Fossan et al. 2021[17]	90 patients	Measured FFR value	CCTA images	Calculated FFR value	Simulations based on the 3D incompressible Navier-Stokes equation, FFR3D, and NN-backed FFRsimple	Not applicable	Purely data-driven NN performed better than the physics-based reduced-order model. Predictions by the informed NNs were better than those by the purely data-driven NN.
Cho et al. 2019[30]	1,501 patients with 1,501 intermediate lesions	Measured FFR value	24 computed angiographic features and four clinical features	FFR < 0.8 or > 0.8	Angiographic images segmented using edge detection; data fed to XGBoost network	Not applicable due to required feature engineering	Angiography-based ML showed good diagnostic performance in identifying ischemia-producing lesions, with FFR ≤ 0.80 predicted with 84% sensitivity, 80% specificity, and 82% overall accuracy.
Mahendiran et al. 2022[31]	83 patients, 200 lesions producing 746 cropped ICA images of future culprit and non-culprit lesions	Actual patient condition	ICA image patches, two angiographic views separated by at least 25°	Future culprit lesion or non-culprit lesion	ResNet18	Not applicable due to required feature engineering	DL outperformed human visual assessment and established angiographic parameters in predicting future culprit lesions.
Zhao et al. 2021[32]	137,126 images from 5,913 angiographic runs of 2,407 patients used	CFR_{manual} calculated using frame count	ICA video with and without hyperemia of the same angiographic projection	Calculated CFR value	CNN with segmentation	18.1 ± 10.3 seconds	Automatic CFR computation using coronary angiography was feasible and showed moderate agreement with manual computation based on frame count.
Carson et al. 2020[33]	Single-vessel and multi-vessel networks from a virtual patient database, and 25 clinically invasive FFR measurements from real patients	Generated and measured FFR values	One-dimensional hemodynamic model	Calculated FFR value	Multivariate Polynomial Regression, Feedforward Neural Network, Long Short-Term Memory against Computational Fluid Dynamics	Not applicable	MPR struggled and produced some erroneous predictions. LSTM performed well for single-vessel cases. FFNN performed well for all cases.
Sun et al. 2022[34]	3,028 idealized stenosis models for training, 324 cases for testing	Measured FFR value	Vascular geometric parameters and blood flow obtained from CCTA	Stenosis resistance	Back propagation neural network	The calculation time for BPNN was approximately 2.15 seconds	Study proposed a method to predict stenosis resistance of coronary arteries rapidly and accurately, which is of great significance for the numerical calculation of FFRCT.

Appendix 1 (cont). Coronary Fractional Flow Reserve Estimation Using Artificial Intelligence Studies

Authors	Dataset	Ground Truth	Input	Output	Method	Computation Time	Results
Muscogiuri et al. 2022[35]	112 patients	Measured FFR value	CTP images	Calculated FFR value	CNN	39.2 ± 3.2 seconds	Evaluation of myocardial ischemia using a DL approach on resting CTP datasets is feasible and accurate.
Xue et al. 2022[36]	40 patients with 67 vessels	Measured FFR value	3D hybrid model using ICA end frame and 2D CCTA model	Calculated FFR value	Multilayer Perceptron Network and Bidirectional Recurrent Neural Network	120 ± 13 seconds	Excellent diagnostic performance in identifying ischemic lesions; may represent an effective and practical alternative to invasive FFR.
Farajtabar et al. 2022[37]	Tested with three real cases	Pressure and velocity distributions over time obtained from FEM-CFD simulation	Geometrical features of the artery and velocity boundary conditions	Pressures and velocities	ANN	Not applicable	Deep neural networks can be a promising alternative to computational fluid dynamics for calculating pressures and velocities in coronary arteries.
Cha et al. 2023[38]	356 lesions from 130 patients	Measured FFR value	Optical Coherence Tomography features	FFR < 0.8 or > 0.8	ML algorithm with additional features (Random Forest)	Not applicable due to required feature engineering	OCT-based ML-FFR demonstrated good diagnostic performance in predicting FFR, irrespective of coronary territory.

AI, Artificial Intelligence; ANN, Artificial Neural Network; CCTA, Cardiac Computed Tomography Angiography; CFD, Computational Fluid Dynamics; CFR, Coronary Flow Reserve; CNN, Convolutional Neural Network; CTP, Computed Tomography Perfusion; DL, Deep Learning; FEM, Finite Element Method; FFNN, Feedforward Neural Network; FFR, Fractional Flow Reserve; ICA, Invasive Coronary Angiography; LAO, Left Anterior Oblique; LCS, Left Coronary System; LSTM, Long Short-Term Memory; MAE, Mean Absolute Error; ML, Machine Learning; MLP, Multilayer Perceptron; MPR, Multivariate Polynomial Regression; NHPR, Non-Hyperemic Pressure Ratio; OCT, Optical Coherence Tomography; QCA, Quantitative Coronary Angiography; RCA, Right Coronary Artery.