EuroIntervention 2021;17:51-58 published online September 2020

Deep learning for prediction of fractional flow reserve from resting coronary pressure curves

Frederik M. Zimmermann[1]*, MD; Thomas P. Mast[1], MD, PhD; Nils P. Johnson[2], MD, MSc; Ivo Everts[3], PhD; Barry Hennigan[4,5], MB BCh BAO; Colin Berry[4,5], MBChB, PhD; Daniel T. Johnson[2], MSc; Bernard De Bruyne[6,7], MD, PhD; William F. Fearon[8], MD; Keith G. Oldroyd[4,5], MD; Nico H.J. Pijls[1,9], MD, PhD; Pim A.L. Tonino[1], MD, PhD; Marcel van 't Veer[1,9], MSc, PhD

1. Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands; 2. Weatherhead PET Center, Division of Cardiology, Department of Medicine, McGovern Medical School at UTHealth and Memorial Hermann Hospital, Houston, TX, USA; 3. GoDataDriven, Amsterdam, the Netherlands; 4. British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; 5. West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, Glasgow, United Kingdom; 6. Cardiovascular Center Aalst, OLV Clinic, Aalst, Belgium; 7. Department of Cardiology, Lausanne University Hospital, Lausanne, Switzerland; 8. Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA; 9. Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00648

KEYWORDS

- fractional flow reserve
- innovation
- stable angina

Abstract

Background: It would be ideal for a non-hyperaemic index to predict fractional flow reserve (FFR) more accurately, given FFR's extensive validation in a multitude of clinical settings.

Aims: The aim of this study was to derive a novel non-hyperaemic algorithm based on deep learning and to validate it in an internal validation cohort against FFR.

Methods: The ARTIST study is a *post hoc* analysis of three previously published studies. In a derivation cohort (random 80% sample of the total cohort) a deep neural network was trained (deep learning) with paired examples of resting coronary pressure curves and their FFR values. The resulting algorithm was validated against unseen resting pressure curves from a random 20% sample of the total cohort. The primary endpoint was diagnostic accuracy of the deep learning-derived algorithms against binary FFR ≤0.8. To reduce the variance in the precision, we used a fivefold cross-validation procedure.

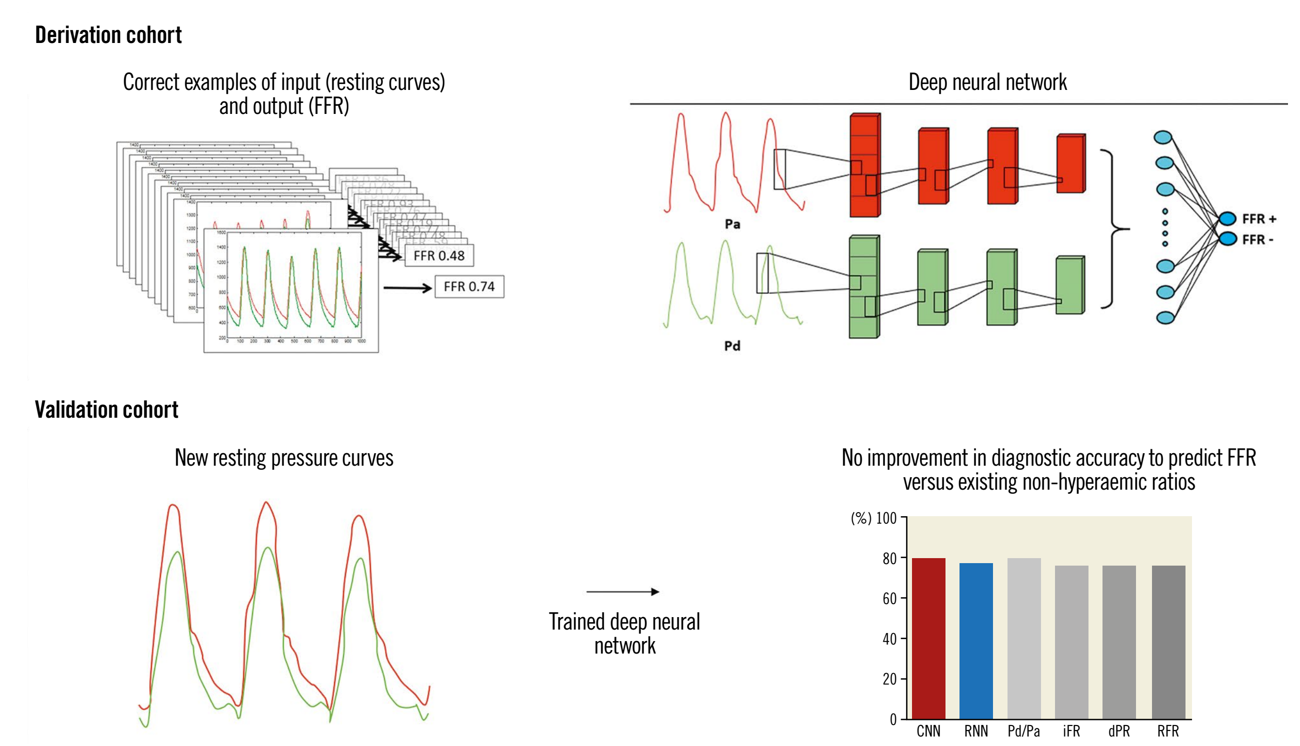
Results: A total of 1,666 patients with 1,718 coronary lesions and 2,928 coronary pressure tracings were included. The diagnostic accuracy of our convolutional neural network (CNN) and recurrent neural networks (RNN) against binary FFR ≤0.80 was 79.6±1.9% and 77.6±2.3%, respectively. There was no statistically significant difference between the accuracy of our neural networks to predict binary FFR and the most accurate non-hyperaemic pressure ratio (NHPR).

Conclusions: Compared to standard derivation of resting pressure ratios, we did not find a significant improvement in FFR prediction when resting data are analysed using artificial intelligence approaches. Our findings strongly suggest that a larger class of hidden information within resting pressure traces is not the main cause of the known disagreement between resting indices and FFR. Therefore, if clinicians want to use FFR for clinical decision making, hyperaemia induction should remain the standard practice.

**Corresponding author: Catharina Hospital Eindhoven, Department of Cardiology, Michelangelolaan 2, 5623 EJ Eindhoven, the Netherlands. E-mail: Frederik.zimmermann@cze.nl*

SUBMITTED ON 19/05/2020 - REVISION RECEIVED ON 1st 01/07/2020 / 2nd 26/08/2020 - ACCEPTED ON 28/08/2020

DOI: 10.4244/EIJ-D-20-00648



Visual summary. *Development and validation of deep neural networks to predict fractional flow reserve (FFR) from resting coronary pressure curves. In a derivation cohort, a deep neural network was trained (deep learning) with examples of resting coronary pressure curves and matching FFR values. After the neural network was trained, its new algorithm was validated using different resting pressure curves. Deep learning-based algorithms did not improve the diagnostic accuracy of predicting FFR compared to other non-hyperaemic indices in a clinically relevant way.*

Abbreviations

CNN	convolutional neural network
dPR	diastolic pressure ratio
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
NHPR	non-hyperaemic pressure ratio
Pa	aortic pressure
Pd	distal coronary pressure
Pd/Pa	resting distal coronary pressure to aortic pressure ratio
RFR	relative flow reserve
RNN	recurrent neural network

Introduction

Fractional flow reserve (FFR) has become the invasive reference standard for assessing the physiological significance of a coronary stenosis based on randomised clinical outcome trials and mechanistic studies[1-4]. Guidance of percutaneous coronary intervention (PCI) by FFR has been shown to be superior to angiography-guided PCI and medical therapy for improving both symptoms and prognosis and is recommended by current guidelines[1-6].

In order to measure FFR, adenosine (or another vasodilator drug) is required to induce hyperaemia, which adds some cost and might cause transient, short-lasting symptoms[1]. Therefore, several non-hyperaemic indices have been proposed that do not require adenosine but are derived from non-hyperaemic (resting) coronary pressure curves[7-10].

Such a resting index usually assesses the pressure ratio during a specific period within the cardiac cycle or focuses on qualitative parameters. Unfortunately, the accuracy of existing non-hyperaemic indices to predict FFR ≤0.80 has consistently been shown to be approximately 80%[7-10].

A possible explanation for this suboptimal predictive value of resting indices is that the information needed to predict FFR from resting curves exists in a more complex and subtle manner beyond simplistic pressure ratios or known qualitative features. In addition, traditional waveform analysis might have limits to discover complex information contained within the pressure curves. However, it would be ideal for a non-hyperaemic index to predict FFR more accurately, given its extensive validation in a multitude of clinical settings.

Deep learning, a subfield of artificial intelligence, can model extremely complicated relationships between inputs and outputs, and has shown potential to improve health care in several areas[11,12]. A deep learning algorithm, a so-called deep neural network, can train itself when provided with a sufficient number of correct examples of input and output. Therefore, we hypothesised that a deep neural network could be trained to predict FFR after

EuroIntervention 2021;17:51-58

receiving many examples of resting pressure curves and their corresponding FFR values.

The aim of this study was to derive a novel non-hyperaemic algorithm based on deep learning and to validate it in an internal validation cohort against FFR.

Methods

STUDY POPULATION

The ARTIST study (ARTificial Intelligence to identify functionally SignificanT coronary stenoses) is a *post hoc* analysis of three previously published studies: CONTRAST (clinicaltrials.gov NCT02184117), VERIFY (clinicaltrials.gov NCT01559493), and VERIFY 2 (clinicaltrials.gov NCT02377310). All studies included in this analysis were approved by the institutional review boards of the individual sites. Detailed descriptions and primary results of these studies have been published previously[13-15]. In short, all three studies recorded raw tracings of simultaneous aortic (Pa) and distal coronary pressure (Pd) during both resting (non-hyperaemic) conditions and maximal hyperaemia induced by either intravenous or intracoronary adenosine.

FRACTIONAL FLOW RESERVE (FFR)

In order to assess FFR uniformly among trials, all hyperaemic pressure curves were anonymised and independently analysed for calculation of smart minimum FFR (smFFR) using an automated algorithm[16] at the Weatherhead PET Imaging Center in Houston, TX, USA. Calculation of smFFR occurred without knowledge of matching non-hyperaemic data.

NON-HYPERAEMIC PRESSURE RATIOS (NHPR)

The following definitions were used to calculate various NHPR – diastolic pressure ratio (dPR): average Pd/Pa from dicrotic notch to 5 ms before end of diastole; resting Pd/Pa: average Pd/Pa over the entire heart cycle; instantaneous wave-free ratio (iFR): average Pd/Pa from 25% into diastole until 5 ms before end of diastole; relative flow reserve (RFR): value at which the filtered ratio of Pd and Pa is lowest during the entire cardiac cycle. According to the literature, a binary cut-off of ≤0.92 was used for resting Pd/Pa and ≤0.89 for other NHPR[8].

DERIVATION COHORT

The **Visual summary** provides an overview of the study design. In a derivation cohort (random 80% sample of the total cohort) a deep neural network was trained (deep learning) with paired examples of resting coronary pressure curves and their FFR values. To reduce the variance in the precision, we used a fivefold cross-validation procedure.

ARTIFICIAL NEURAL NETWORK

A one-dimensional convolutional neural network (CNN) was used to classify resting pressure recordings into FFR positive (FFR ≤0.80) or FFR negative (FFR >0.80) binary categories, and to predict FFR as a continuous outcome. A CNN can automatically learn and identify features that are present among the resting coronary pressure curves[11,12]. The architecture of the CNN consisted of five layers **(Figure 1A)** to provide feature extraction on different levels. Several variations of this CNN architecture were tested **(Supplementary Table 1)**. A detailed description of neural architectures is provided in **Supplementary Appendix 1**.

In addition to a CNN, we tested a different deep learning architecture – a recurrent neural network (RNN) **(Figure 1B)**. An RNN is especially designed to incorporate temporal dependency among features by adding information of a previous interval to the next interval[17]. This contrasts with a CNN, which is insensitive to the temporal location of the feature within the pressure curve itself. Two different RNN variations were used mutually exclusively – long short-term memory cells (LSTM) and gated recurrent units (GRU).

All deep learning models were implemented using scikit-learn in Python™ (Python Software Foundation, Wilmington, DE, USA).

VALIDATION COHORT

After a neural network was trained, its resulting algorithm was validated against unseen resting pressure curves from a random 20% sample of the total cohort. The primary endpoint of the validation cohort was diagnostic accuracy of the deep learning-derived algorithms against binary FFR ≤0.8. In addition, sensitivity, specificity, positive predictive value, and negative predictive value were calculated, with FFR ≤0.80 as reference standard. The diagnostic performance was presented as mean and standard deviation of the fivefold cross-validation procedure.

The diagnostic performance of several non-hyperaemic pressure ratios was also calculated and compared using a McNemar test. A mean and 95% confidence interval for the diagnostic performance was calculated for the non-hyperaemic pressure ratios based on these data.

Prediction of FFR as a continuous variable was analysed using the area under the receiver operating characteristic (ROC) curve (compared using the DeLong method).

Applicable tests were two-tailed, and $p<0.05$ was considered statistically significant. Analysis was conducted using R, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1,666 patients with 1,718 coronary lesions and 2,928 coronary pressure tracings were included. **Supplementary Table 2** summarises the baseline characteristics. Approximately 71% of patients were male, and the majority of patients had one or more classic risk factors for coronary artery disease. Baseline characteristics and angiographic data in the individual trials have been reported previously[13-15]. **Supplementary Figure 1** shows density plots of FFR and several non-hyperaemic pressure ratios of our pooled cohort. Median resting Pd/Pa was 0.92 (interquartile range [IQR] 0.88-0.96), median iFR was 0.89 (IQR 0.83-0.94), and median FFR was 0.80 (IQR 0.72-0.86). Out of 1,718 coronary lesions, 923 (54%) had FFR ≤0.80.

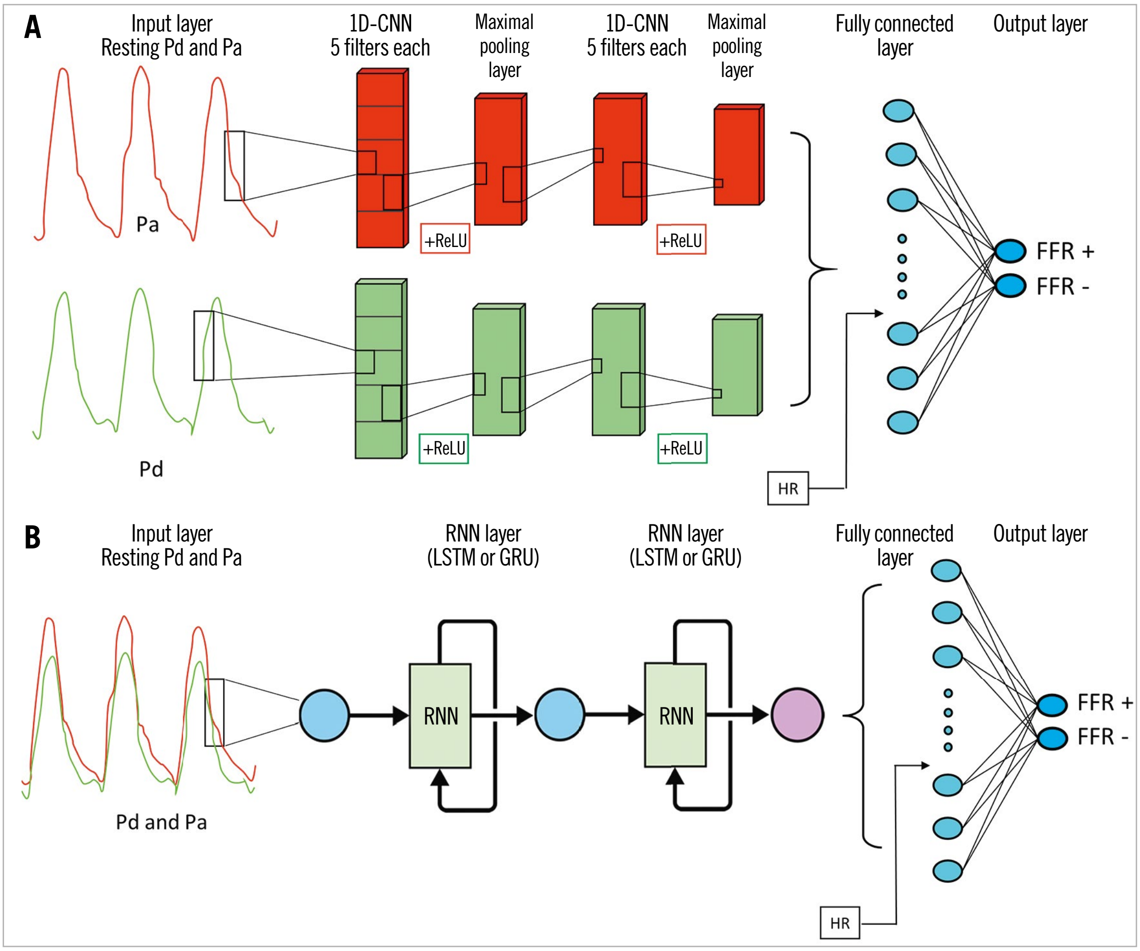


Figure 1. *Detailed architecture of deep neural networks. A) CNN. B) RNN. CNN: convolutional neural network; FFR: fractional flow reserve; GRU: gated recurrent unit; HR: heart rate; LSTM: long short-term memory; Pa: aortic pressure; Pd: distal coronary pressure; ReLU: rectified linear unit; RNN: recurrent neural network*

ENDPOINTS

Figure 2 shows the diagnostic performance of our deep neural architectures compared to FFR. Diagnostic accuracy (acc), sensitivity (sens), specificity (spec), positive predictive value (PPV), and negative predictive value (NPV) of our CNN against binary FFR ≤0.80 using fivefold cross-validation was 79.6±1.9%, 81.5±3.2%, 77.1±6.4%, 80.6±3.6%, and 78.5±2.4%, respectively. Acc, sens, spec, PPV, and NPV for our RNN against FFR using fivefold cross-validation were 77.6±2.3%, 73.8±6.1%, 81.5±6.4%, 82.6±3.5%, and 73.4±3.8%, respectively.

The diagnostic accuracy of NHPR was 79.7% for Pd/Pa, 76.1% for iFR, 76.4% for dPR, and 76.3% for RFR. There was no statistically significant difference between the diagnostic accuracy of both neural networks and the NHPR with the highest accuracy (Pd/Pa), p>0.40 for both comparisons. Optimal cut-off values for existing NHPR to predict binary FFR ≤0.80 in our large cohort were near identical to published cut-off values **(Supplementary Table 3)**.

As detailed in **Supplementary Figure 2**, the area under the ROC curve of our CNN and RNN was 0.88 and 0.84, respectively. Compared to other NHPR, the AUC of the CNN was larger compared to 0.86 for Pd/Pa, 0.84 for iFR, 0.85 for dPR, and 0.85 for RFR (DeLong p<0.01 vs other NHPR), although neither analysis was pre-specified or adjusted for multiple comparisons **(Supplementary Table 4)**. Sensitivity analyses using 16 variations in CNN and RNN architectures did not result in an increase in the diagnostic performance against binary FFR ≤0.80 **(Supplementary Table 1)**. In addition, a pressure recording-level analysis (multiple pressure recordings per lesions allowed) or patient-level analysis (randomly selecting one coronary lesion per patient in case of multiple lesions per patient; ~4% of patients) instead of a lesion-level analysis did not alter the diagnostic performance.

Discussion

The ARTIST study is the first to assess deep learning for the prediction of FFR from resting coronary pressure curves. We found that deep learning-based algorithms did not improve the diagnostic accuracy of predicting FFR compared to other non-hyperaemic indices in a clinically relevant way. Our findings eliminate a larger class of possible hidden information than has been examined before. Therefore, inducing maximal hyperaemia remains a prerequisite for accurate FFR assessment.

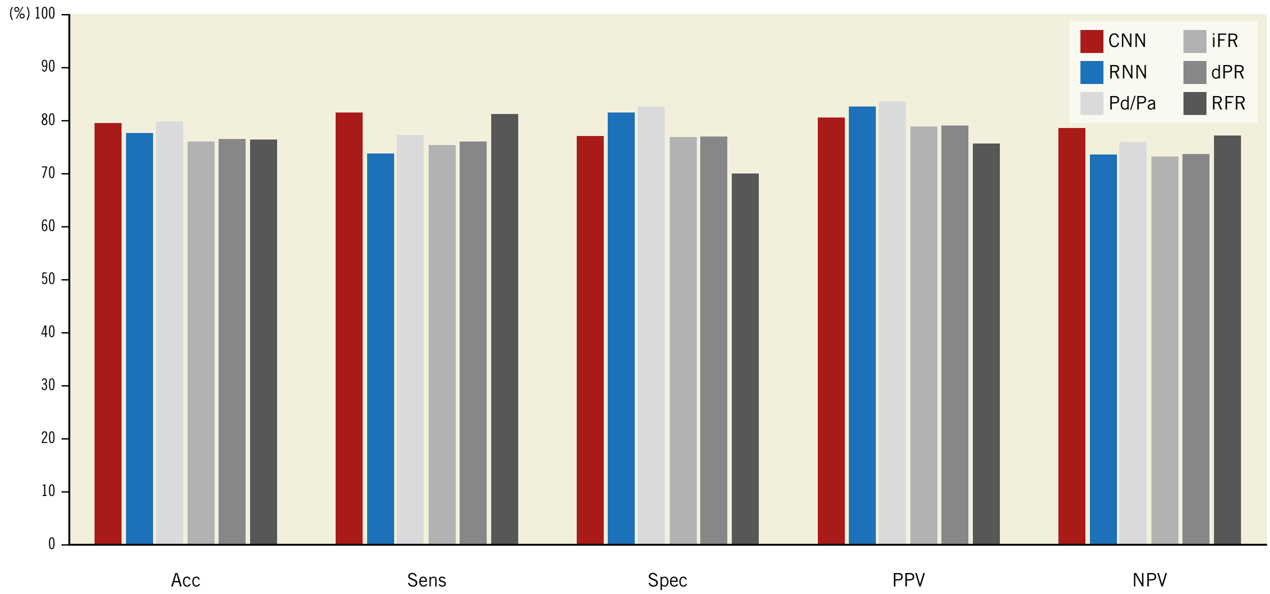


Figure 2. *Diagnostic performance of our deep learning-based algorithms and other NHPRs, against binary FFR ≤0.80 (diagnostic accuracy of both neural networks not statistically different against the most accurate NHPR). Acc: accuracy; CNN: convolutional neural network; dPR: diastolic pressure ratio; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; NPV: negative predictive value; Pd/Pa: ratio of distal coronary pressure to aortic pressure; PPV: positive predictive value; RFR: relative flow reserve; RNN: recurrent neural network; Sens: sensitivity; Spec: specificity*

THE NEED FOR FFR (PREDICTION) IN THE ERA OF NHPR

Recently, two large randomised clinical trials have demonstrated that iFR-guided PCI (one of several NHPR) is non-inferior to FFR-guided PCI in a low-risk population at maximal two-year follow-up, when including ~80% of concordant FFR/iFR cases[9,18,19]. Although NHPRs are a welcome addition to the interventional armamentarium to assess coronary physiology in such low-risk populations, it is still desirable to measure FFR itself (or predict it accurately) for several reasons. First, only FFR has been tested against a true gold standard of myocardial ischaemia[1]. Second, FFR is the only index that has been proven superior to both medical therapy and angio-guided PCI in randomised clinical trials with follow-up extending to 15 years[2-4]. Third, FFR has been clinically validated in many subgroups, including non-culprit lesions of acute coronary syndromes, left main disease, pre-coronary bypass surgery, and bifurcation lesions[2-4,20-22]. Finally, the clinical benefit and safety of FFR-guided PCI has been tested not only in randomised trials, but also in large real-world observational studies[23,24]. For example, in the randomised DEFINE-FLAIR study on iFR, only about half of PCIs were guided by physiology, related to the protocol-based requirement to confine physiology assessment to lesions with 40-70% diameter stenosis[9]. How NHPRs perform in a real-world setting, including frequently occurring 70-90% lesions, remains an important yet unanswered clinical question.

THE QUEST FOR HIDDEN INFORMATION IN RESTING CORONARY PRESSURE CURVES

Over the past decade, there has been increasing interest in predicting FFR from resting coronary pressure curves, aiming at simplifying the procedure and preventing the need for adenosine[7-9]. During this time, the results of multiple studies in this field can be summarised by two simple conclusions. First, all proposed NHPRs are numerically equivalent. Second, the diagnostic accuracy of NHPRs to predict binary FFR ≤0.80 is around 80% regardless of the timing within the cardiac cycle[7-9].

In order to create a non-hyperaemic index that is able to predict FFR more accurately, the ARTIST study was designed to overcome limitations of previous studies. **Supplementary Table 5** summarises the potential advantages of our design compared to pivotal studies in this field.

First, ARTIST was structured to create a new index with the highest possible agreement with FFR, in contrast to several previous studies that only validated an existing index.

Second, almost all previous studies focused only on the ratio of distal to aortic pressure during a specific period of the cardiac cycle and neglected qualitative information. For example, it is known that the distal coronary pressure curve changes, not only numerically, but also in morphology with increasing stenosis severity[10]. Only two previous studies incorporated pre-specified qualitative features, such as the presence of the dicrotic notch and diastolic dipping[10] or wave-intensity analysis[25], without significant success. Although some of these qualitative features were chosen on a physiological basis, such assumptions neglect the existence of possible additional information outside of the underlying theory.

Third, to the best of our knowledge, this study was the first to use deep learning to predict FFR from resting pressure curves. Over recent years, deep neural networks have shown impressive results in several areas of medicine[11,12]. A deep neural network uses multiple layers to abstract features on different levels of the data[12]. As such, even non-pre-specified features have the potential to be identified. Therefore, we hypothesised that deep learning would be capable of identifying complex interactions among features contained in the resting pressure curve that might be pivotal to predicting FFR more accurately.

Finally, ARTIST was among the largest cohorts to date studying the prediction of FFR from resting coronary pressure curves.

Despite these numerous advantages in study design, including the use of deep learning, the current study reached an accuracy to predict FFR of approximately 80%, in accordance with previously reported NHPRs.

Given the small changes in AUC as shown in **Supplementary Figure 2** among NHPRs largely considered to be clinically equivalent (largest delta 0.02, with baseline Pd/Pa actually having the largest AUC) and lack of pre-specification between CNN and RNN architectures (delta 0.04 between the two methods), we feel that the statistically larger AUC for CNN versus other NHPRs (deltas 0.02 to 0.04) should not be overinterpreted as providing a meaningful clinical advantage.

WHY IS IT NOT POSSIBLE TO PREDICT FFR ACCURATELY FROM RESTING PRESSURE CURVES?

Several factors might explain why FFR cannot be predicted accurately from resting coronary pressure curves. The hyperaemic trans-stenotic pressure gradient is dependent on several unpredictable factors, including hyperaemic coronary flow and a complex stenosis-specific pressure-flow relationship[26,27]. Beyond epicardial disease, hyperaemic coronary flow is mostly dependent on the amount of myocardial mass and microvascular function, which appear to be unpredictable from resting coronary pressure curves. The pressure-flow relationship between the trans-stenotic pressure gradient (ΔP) and average whole-cycle flow is a curvilinear function: $\Delta P = f \cdot Q + s \cdot Q^2$ [26,27]. This relationship is dependent on both friction (f) and separation (s) pressure loss. Both coefficients depend on vessel size, stenosis geometry, and blood rheology[26,27], which apparently do not affect resting coronary pressure morphology in a way that can be picked up by a neural network. Future studies might increase the diagnostic accuracy of deep learning-based algorithms when incorporating additional information such as stenosis geometry or myocardial mass. In addition, if one could measure the pressure gradient at different flow rates, then one could assess the corresponding pressure-flow relationship. Since the resting pressure gradient is obtained only at single flow rate, predictions about hyperaemic conditions cannot be made with acceptable precision. Finally, it would be of interest for future deep learning models to incorporate clinical outcome. These models might be able to find hidden information in (non-)hyperaemic curves useful to predict future events or symptoms.

We observed a lower accuracy in CNNs including a rectified linear unit (ReLU). One of the potential advantages of using a ReLU is that it decreases overfitting in complex data sets, although some information is lost in the process. It might be possible that useful information to predict FFR was lost due to the ReLU, although this might also be related to a play of chance.

Limitations

This study has several limitations. First, this was a *post hoc* analysis. Second, although our cohort is the largest reported to predict FFR from resting coronary pressure curves, deep learning usually requires huge amounts of data to function optimally. Nevertheless, given the fact that our results do not provide a hint for a possible improvement in accuracy, we believe that a much bigger cohort would not change the conclusion of this paper relevantly. Third, although we already tested multiple deep neural architectures, it cannot be excluded that other architectures would yield a different result. However, given the near identical accuracy between the architectures used in our study, we do not expect that a different architecture would increase the predictable value in a clinically meaningful manner.

Conclusions

Compared to standard derivation of resting pressure ratios, we did not find a significant improvement in FFR prediction when resting data are analysed using artificial intelligence approaches. Our findings strongly suggest that a larger class of hidden information within resting pressure traces is not the main cause for the known disagreement between resting indices and FFR. Therefore, if clinicians want to use FFR for clinical decision making, hyperaemia induction should remain the standard practice.

Impact on daily practice

Regardless of the use of deep learning, the diagnostic accuracy to predict FFR from resting coronary pressure curves is around 80%. Therefore, inducing maximal hyperaemia remains a prerequisite for accurate FFR assessment. Adding clinical information or (non-invasive) anatomical information might increase the diagnostic performance of future deep learning models at the cost of greater complexity for the user.

Funding

ARTIST was an investigator-initiated study supported by an unrestricted research grant from Top Medical BV, Esloo, the Netherlands. Deep learning analyses were performed by Medicx.AI, part of GoDataDriven, Amsterdam, the Netherlands.

Conflict of interest statement

B. De Bruyne reports grants from Abbott, Boston Scientific, and Biotronik, and institutional consultancy for Opsens, Boston Scientific, and Abbott, outside the submitted work. C. Berry reports non-financial support from Coroventis, during the conduct of the study; non-financial support from Abbott Vascular, and non-financial support and other from HeartFlow, outside the submitted work. I. Everts reports being a full-time employee of GoDataDriven, which created the AI algorithm used in the study. N.P. Johnson reports an institutional licensing agreement with Boston Scientific, Volcano/Philips, and St. Jude Medical, outside the submitted work. In addition, he has a patent pending on quantification of aortic valve stenosis (SAVI). N.H.J. Pijls reports grants and personal fees from Abbott and Opsens, outside the submitted work. K.G. Oldroyd reports grants and personal fees from Abbott Vascular, outside the submitted work. W.F. Fearon reports grants from Abbott Vascular, Medtronic, CathWorks, and ACIST Medical, personal fees from Boston Scientific, and minor stock options from HeartFlow, outside the submitted work. The other authors have no conflicts of interest to declare.

References

1. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703-8.

2. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, Erbel R, Legrand V, Gwon HC, Remkes WS, Stella PR, van Schaardenburgh P, Bech GJ, De Bruyne B, Pijls NH. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J.* 2015;36:3182-8.

3. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, Engstrøm T, Kääb S, Dambrink JH, Rioufol G, Toth GG, Piroth Z, Witt N, Fröbert O, Kala P, Linke A, Jagic N, Mates M, Mavromatis K, Samady H, Irimpen A, Oldroyd K, Campo G, Rothenbühler M, Jüni P, De Bruyne B; FAME 2 Investigators. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med.* 2018;379:250-9.

4. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engstrøm T, Klauss V, MacCarthy PA, Manoharan G, Oldroyd KG, Ver Lee PN, Van't Veer M, Fearon WF, De Bruyne B, Pijls NH; FAME Study Investigators. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet.* 2015;386:1853-60.

5. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2014;130:1749-67.

6. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41:407-77.

7. Van't Veer M, Pijls NHJ, Hennigan B, Watkins S, Ali ZA, De Bruyne B, Zimmermann FM, van Nunen LX, Barbato E, Berry C, Oldroyd KG. Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal? *J Am Coll Cardiol.* 2017;70:3088-96.

8. De Maria GL, Garcia-Garcia HM, Scarsini R, Hideo-Kajita A, Gonzalo López N, Leone AM, Sarno G, Daemen J, Shlofmitz E, Jeremias A, Tebaldi M, Bezerra HG, Tu S, Lemos PA, Ozaki Y, Dan K, Collet C, Banning AP, Barbato E, Johnson NP, Waksman R. Novel Indices of Coronary Physiology: Do We Need Alternatives to Fractional Flow Reserve? *Circ Cardiovasc Interv.* 2020;13:e008487.

9. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Härle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med.* 2017;376:1824-34.

10. Matsumura M, Maehara A, Johnson NP, Fearon WF, De Bruyne B, Oldroyd KG, Pijls NHJ, Jenkins P, Ali ZA, Mintz GS, Stone GW, Jeremias A. Qualitative resting coronary pressure wave form analysis to predict fractional flow reserve. *EuroIntervention.* 2019;14:e1601-8.

11. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, Carter RE, Yao X, Rabinstein AA, Erickson BJ, Kapa S, Friedman PA. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet.* 2019;394:861-7.

12. Hinton G. Deep Learning-A Technology With the Potential to Transform Health Care. *JAMA.* 2018;320:1101-2.

13. Johnson NP, Jeremias A, Zimmermann FM, Adjedj J, Witt N, Hennigan B, Koo BK, Maehara A, Matsumura M, Barbato E, Esposito G, Trimarco B, Rioufol G, Park SJ, Yang HM, Baptista SB, Chrysant GS, Leone AM, Berry C, De Bruyne B, Gould KL, Kirkeeide RL, Oldroyd KG, Pijls NHJ, Fearon WF. Continuum of Vasodilator Stress From Rest to Contrast Medium to Adenosine Hyperemia for Fractional Flow Reserve Assessment. *JACC Cardiovasc Interv.* 2016;9:757-67.

14. Berry C, van 't Veer M, Witt N, Kala P, Bocek O, Pyxaras SA, McClure JD, Fearon WF, Barbato E, Tonino PA, De Bruyne B, Pijls NH, Oldroyd KG. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. *J Am Coll Cardiol.* 2013;61:1421-7.

15. Hennigan B, Oldroyd KG, Berry C, Johnson N, McClure J, McCartney P, McEntegart MB, Eteiba H, Petrie MC, Rocchiccioli P, Good R, Lindsay MM, Hood S, Watkins S. Discordance Between Resting and Hyperemic Indices of Coronary Stenosis Severity: The VERIFY2 Study (A Comparative Study of Resting Coronary Pressure Gradient, Instantaneous Wave-Free Ratio and Fractional Flow Reserve in an Unselected Population Referred for Invasive Angiography). *Circ Cardiovasc Interv.* 2016;9:e004016.

16. Johnson NP, Johnson DT, Kirkeeide RL, Berry C, De Bruyne B, Fearon WF, Oldroyd KG, Pijls NHJ, Gould KL. Repeatability of Fractional Flow Reserve Despite Variations in Systemic and Coronary Hemodynamics. *JACC Cardiovasc Interv.* 2015; 8:1018-27.

17. Choi E, Schuetz A, Stewart WF, Sun J. Using recurrent neural network models for early detection of heart failure onset. *J Am Med Inform Assoc*. 2017;24:361-70.

18. Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Öhagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Tödt T, Venetsanos D, James SK, Kåregren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Fröbert O; iFR-SWEDEHEART Investigators. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med.* 2017;376:1813-23.

19. Pijls NHJ, De Bruyne B. Instantaneous Wave-free Ratio versus Fractional Flow Reserve. *N Engl J Med.* 2017;377:1596.

20. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med.* 2017;376:1234-44.

21. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L; DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet.* 2015;386:665-71.

22. Johnson NP, Gould KL, Di Carli MF, Taqueti VR. Invasive FFR and Noninvasive CFR in the Evaluation of Ischemia: What Is the Future? *J Am Coll Cardiol.* 2016;67: 2772-88.

23. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, Kim JH, Chae IH, Yoon JH, Her SH, Seung KB, Chung WY, Yoo SY, Lee JB, Choi SW, Park K, Hong TJ, Lee SY, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park SJ; IRIS-FFR Investigators. Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation.* 2017;135: 2241-51.

24. Li J, Elrashidi MY, Flammer AJ, Lennon RJ, Bell MR, Holmes DR, Bresnahan JF, Rihal CS, Lerman LO, Lerman A. Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice. *Eur Heart J.* 2013;34:1375-83.

25. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J,

Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol.* 2012;59:1392-402.

26. Choy JS, Kassab GS. Scaling of myocardial mass to flow and morphometry of coronary arteries. *J Appl Physiol* (1985). 2008;104:1281-6.

27. Zimmermann FM, Pijls NHJ, De Bruyne B, Bech GJ, van Schaardenburgh P, Kirkeeide RL, Gould KL, Johnson NP. What can intracoronary pressure measurements tell us about flow reserve? Pressure-Bounded coronary flow reserve and example application to the randomized DEFER trial. *Catheter Cardiovasc Interv.* 2017;90:917-25.

Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Figure 1. Density plots of FFR and several non-hyperaemic pressure ratios.

Supplementary Figure 2. Receiver operating characteristic curve (ROC) of several indices to predict binary FFR ≤0.80.

Supplementary Table 1. Diagnostic performance of 16 deep learning-based architectures against binary FFR ≤0.80.

Supplementary Table 2. Baseline characteristics.

Supplementary Table 3. Diagnostic performance (%) of existing non-hyperaemic pressure ratios, using both published cut-off values and optimal cut-off in our cohort to predict binary FFR ≤0.80.

Supplementary Table 4. Area under the receiver operating characteristic curve (AUC) to predict binary FFR ≤0.80 (compared using the DeLong method).

Supplementary Table 5. Comparison of the potential advantages in design of the ARTIST study with pivotal studies on the prediction of FFR from resting coronary pressure curves.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00648

Supplementary data

Supplementary Appendix 1. Methods

Deep learning architectures – pre-processing

The input data set consisted of simultaneous recordings of both the resting distal coronary pressure and the aortic pressure. All recordings were resampled to 100 Hz. Three consecutive cardiac cycles were randomly selected from each resting (non-hyperaemic) recording. In order to overcome differences in heart rate, a temporal alignment procedure was performed by resampling all data to 60 samples per cardiac cycle leading to a total of 180 samples per input. Information on heart rate was available in the raw tracing but was lost in this process of resampling. For this reason, the heart rate was extracted from the raw tracings and added in the final layer of the neural network. The neural networks were trained solely on resting pressure curves and no additional features were included.

Artificial neural network

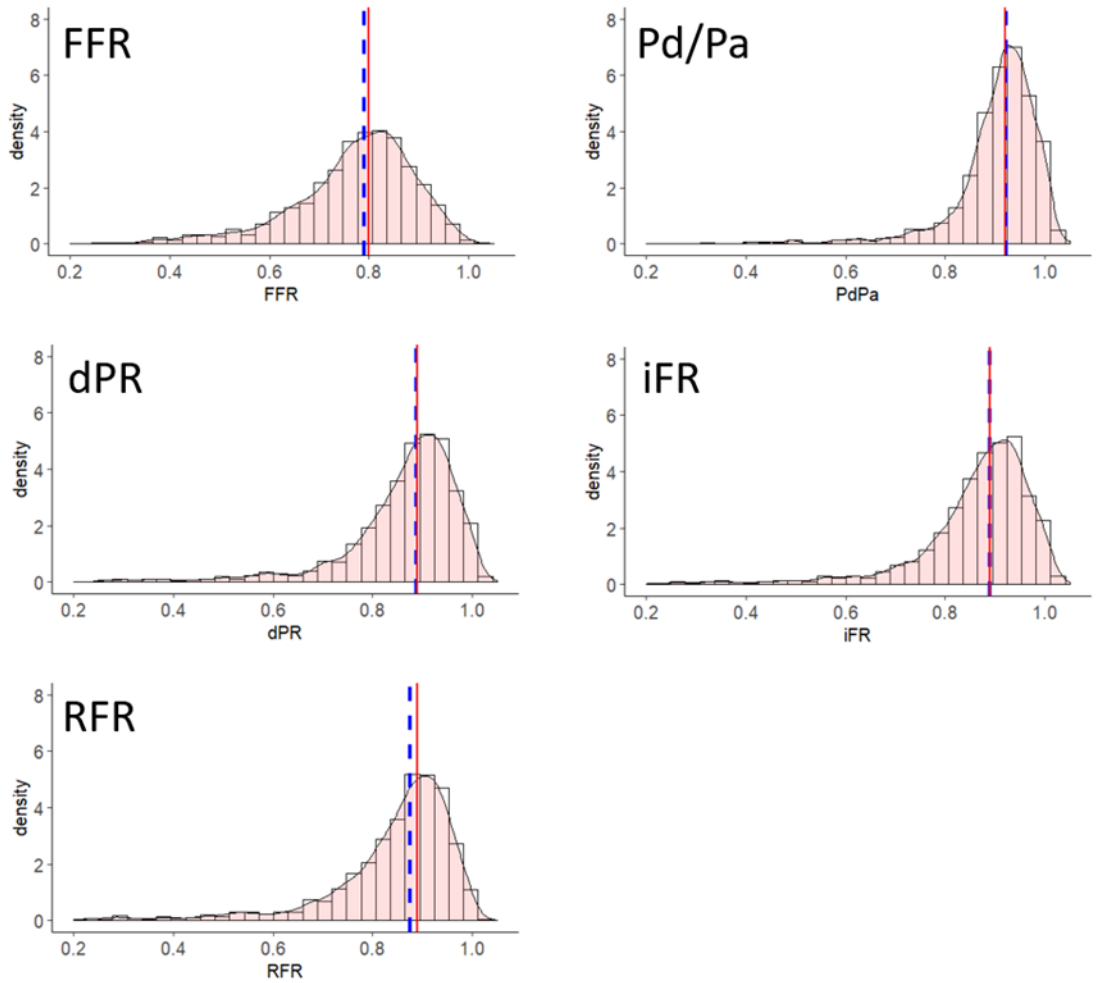
A one-dimensional convolutional neural network (CNN) was used to classify resting pressure recordings into FFR positive (FFR ≤0.80) or FFR negative (FFR >0.80) binary categories, and to predict FFR as a continuous outcome. A CNN can automatically learn and identify features that are present among the resting coronary pressure curves [11,12]. The architecture of the CNN consisted of five layers **(Figure 2A)**. Feature extraction was performed by the first convolutional layer consisting of five input filters for each pressure curve. Input filter size was 30 samples (i.e., a half cardiac cycle). The second layer was a maximal pooling layer (down sampling by order of 2) to extract dominant features from the data and to prevent overfitting. Next, the results were fed into a second convolutional layer with a subsequent maximal pooling layer to extract features at a higher level of abstraction. A rectified linear units (ReLU) activation function was applied to both convolutional layers. Heart rate during rest was extracted from the raw tracings and incorporated into the final layer. The final layer was a fully connected layer with sigmoid activation to transform the features into the final output (or classification): FFR+ (FFR ≤0.80) or FFR– (FFR >0.80).

Several variations of this CNN architecture were tested **(Supplementary Table 1)**: inclusion and exclusion of ReLU activation, addition of a second convolutional layer, filter size of 30 versus 60, and including and excluding heart rate.

In addition to a CNN, we tested a different deep learning architecture - a recurrent neural network (RNN) **(Figure 2B)**. A recurrent neural network is especially designed to incorporate temporal dependency among features by adding information of a previous interval to the next interval [17]. This contrasts with a CNN, which is insensitive to the temporal location of the feature within the pressure curve itself. Two different RNN variations were used mutually exclusively: long short-term memory cells (LSTM) and gated recurrent units (GRU). The first temporal feature extraction was performed by an RNN layer which used the combined Pd/Pa pressure curve as input. The second layer was another RNN layer to extract additional features on different time scales. A fully connected layer acted as the final layer with sigmoid activation and was mapped to the final output (or classification): FFR+ (FFR ≤0.80) or FFR– (FFR >0.80). Heart rate during rest was extracted from the raw tracings and incorporated into the final layer. Several variations of this RNN architecture were tested by varying the number of RNN layers, LSTM versus GRU, and by including and excluding heart rate **(Supplementary Table 1)**.

For predicting FFR as a continues outcome, the models were trained with the absolute FFR values as outcome. The mean squared error between ground truth (FFR) and predictions was now taken as the optimisation criterion, as opposed to binary cross entropy in the case of predicting binary FFR ≤0.80.

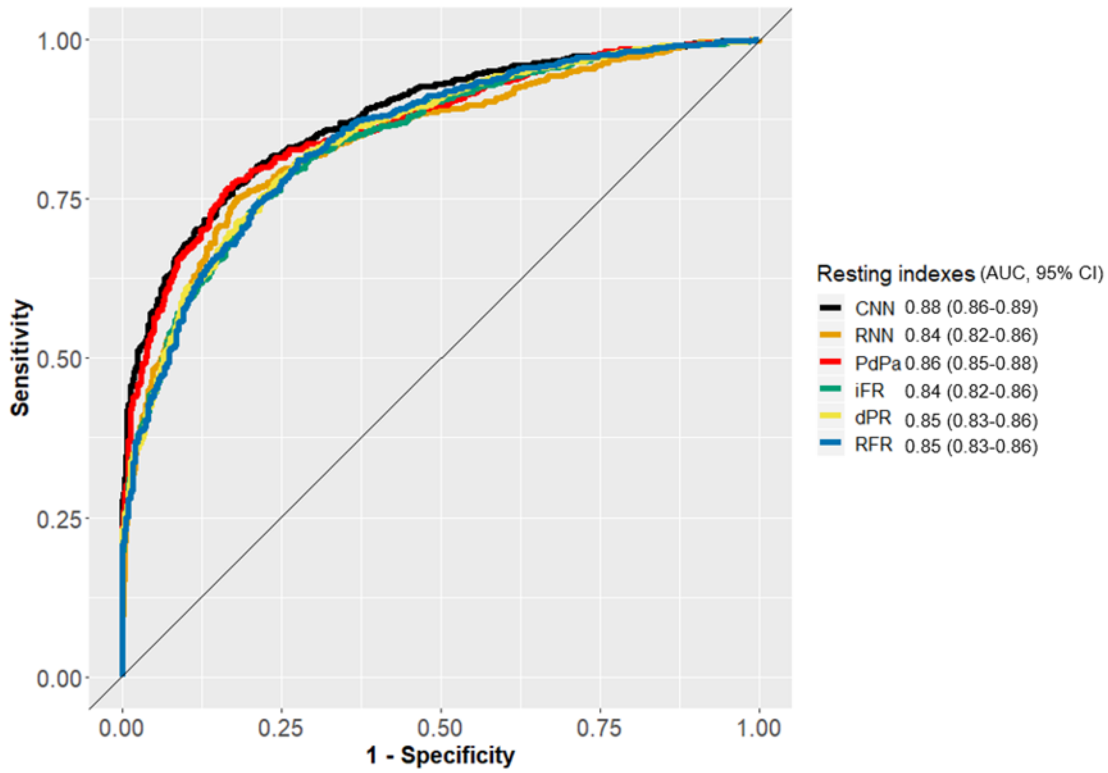
Both CNN and RNN were trained using 4,000 epochs; at each epoch the models were fed in batches of 64. All deep learning models were implemented using scikit-learn in Python™.



Supplementary Figure 1. Density plots of FFR and several non-hyperaemic pressure ratios.

Blue dashed line represents median. Red line represents published cut-off value.

dPR: diastolic pressure ratio; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; NHPR: non-hyperaemic pressure ratio; Pd/Pa: resting distal coronary pressure to aortic pressure ratio; RFR: relative flow reserve



Supplementary Figure 2. Receiver operating characteristic curve (ROC) of several indices to predict binary FFR ≤0.80.

AUC: area under the receiver operating characteristic curve; CI: confidence interval; CNN: convolutional neural network; dPR: diastolic pressure ratio; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; Pd/Pa: resting distal coronary pressure to aortic pressure ratio; RFR: relative flow reserve; RNN recurrent neural network

Supplementary Table 1. Diagnostic performance of 16 deep learning-based architectures against binary FFR ≤0.80.

	Neural network	Hidden conv. layers	Hidden RNN layers	Filter size	ReLU	GRU or LSTM	HR	Acc*	Sens*	Spec*	PPV*	NPV*
1	CNN	1	N/A	60	No	N/A	No	0.79 ±0.03	0.75 ±0.08	0.83 ±0.06	0.83 ±0.05	0.75 ±0.07
2	CNN	1	N/A	60	No	N/A	Yes	0.79 ±0.02	0.80 ±0.03	0.78 ±0.07	0.80 ±0.05	0.77 ±0.03
3	CNN	1	N/A	60	Yes	N/A	No	0.76 ±0.02	0.75 ±0.06	0.78 ±0.04	0.79 ±0.03	0.73 ±0.03
4	CNN	1	N/A	60	Yes	N/A	Yes	0.75 ±0.05	0.75 ±0.06	0.75 ±0.09	0.78 ±0.08	0.73 ±0.03
5	CNN	2	N/A	30	No	N/A	No	0.79 ±0.02	0.80 ±0.04	0.78 ±0.07	0.81 ±0.05	0.77 ±0.04
6	CNN	2	N/A	30	No	N/A	Yes	0.80 ±0.02	0.82 ±0.03	0.77 ±0.06	0.81 ±0.04	0.79 ±0.02
7	CNN	2	N/A	30	Yes	N/A	No	0.71 ±0.09	0.65 ±0.18	0.78 ±0.11	0.76 ±0.12	0.67 ±0.07
8	CNN	2	N/A	30	Yes	N/A	Yes	0.71 ±0.09	0.74 ±0.08	0.66 ±0.12	0.72 ±0.12	0.69 ±0.07
9	RNN	N/A	1	N/A	N/A	GRU	No	0.78 ±0.02	0.74 ±0.06	0.81 ±0.06	0.83 ±0.04	0.73 ±0.04
10	RNN	N/A	1	N/A	N/A	GRU	Yes	0.74 ±0.04	0.70 ±0.09	0.79 ±0.04	0.79 ±0.04	0.70 ±0.07
11	RNN	N/A	1	N/A	N/A	LSTM	No	0.77 ±0.02	0.74 ±0.05	0.80 ±0.06	0.81 ±0.03	0.73 ±0.03
12	RNN	N/A	1	N/A	N/A	LSTM	Yes	0.74 ±0.04	0.71 ±0.10	0.79 ±0.06	0.79 ±0.05	0.71 ±0.08
13	RNN	N/A	2	N/A	N/A	GRU	No	0.75 ±0.03	0.75 ±0.06	0.76 ±0.07	0.82 ±0.10	0.73 ±0.04
14	RNN	N/A	2	N/A	N/A	GRU	Yes	0.77 ±0.01	0.81 ±0.02	0.72 ±0.02	0.77 ±0.02	0.77 ±0.02
15	RNN	N/A	2	N/A	N/A	LSTM	No	0.76 ±0.03	0.76 ±0.06	0.75 ±0.06	0.78 ±0.05	0.74 ±0.05
16	RNN	N/A	2	N/A	N/A	LSTM	Yes	0.77 ±0.01	0.81 ±0.02	0.73 ±0.01	0.77 ±0.02	0.77 ±0.03

*Using fivefold cross-validation.

±: standard deviation; Acc: accuracy; CNN: convolutional neural network; conv: convolutional; GRU: gated recurrent unit; HR: heart rate; LSMT: long short-term memory; N/A: not applicable; NPV: negative predictive value; PPV: positive predictive value; RNN: recurrent neural network; ReLU: rectified linear unit; Sens: sensitivity; Spec: specificity

Supplementary Table 2. Baseline characteristics.

Number of subjects	1,666
Number of lesions	1,718
Number of pressure recordings	2,928
Clinical	
Age, yrs	64.6±10.1
Male	829/1,166 (71.1%)
Body mass index, kg/m^2 *	27.4±4.7
Smoking #	475/1,166 (40.7%)
Hypertension #	805/1,166 (69.0%)
Dyslipidaemia #	768/1,166 (65.9%)
Diabetes mellitus #	300/1,166 (25.7%)
Family history of CAD #	384/1,166 (32.9%)
Previous MI #	271/960 (28.2%)
Previous PCI #	169/960 (17.6%)
Artery	
LM #	34/1,226 (2.8%)
LAD #	747/1,226 (60.9%)
LCx #	215/1,226 (17.5%)
RCA #	230/1,226 (18.8%)
Physiology	
FFR	0.80 (0.72-0.86)
FFR ≤0.80	923/1,718 (54%)
Pd/Pa	0.92 (0.88-0.96)
dPR	0.89 (0.83-0.93)
RFR	0.88 (0.81-0.92)

Values are mean±SD, median (IQR) or n (%) as appropriate.

* data were not reported by the VERIFY-2 study.

data were not or only partially reported by the VERIFY study.

CAD: coronary artery disease; dPR: diastolic pressure ratio; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LM: left main coronary artery; MI: myocardial infarction; RCA: right coronary artery; PCI: percutaneous coronary intervention; Pd/Pa: resting distal coronary pressure to aortic pressure ratio; RFR: relative flow reserve

Supplementary Table 3. Diagnostic performance (%) of existing non-hyperaemic pressure ratios, using both published cut-off values and optimal cut-off in our cohort to predict binary FFR ≤0.80.

	Using published cut-off value						**Using optimal cut-off in this cohort to predict binary FFR ≤0.80**					
Index	**Cut-off**	**Acc**	**Sens**	**Spec**	**PPV**	**NPV**	**Cut-off**	**Acc**	**Sens**	**Spec**	**PPV**	**NPV**
Pd/Pa	0.92	79.7	77.2	82.6	83.6	75.9	0.919	79.8	76.5	83.6	84.2	75.6
iFR	0.89	76.1	75.4	76.9	79.0	73.2	0.889	76.5	74.8	78.5	80.0	73.1
RFR	0.89	76.4	76.1	77	79.1	73.7	0.887	77.0	81.0	72.4	77.1	76.9
dPR	0.89	76.3	81.2	69.9	75.7	77.1	0.892	77.0	77.8	76.0	78.8	74.9

Acc: accuracy; CNN: convolutional neural network; dPR: diastolic pressure ratio; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; NPV: negative predictive value; Pd/Pa: ratio of distal coronary pressure to aortic pressure; PPV: positive predictive value; RFR: relative flow reserve; RNN: recurrent neural network; Sens: sensitivity; Spec: specificity

Supplementary Table 4. Area under the receiver operating characteristic curve (AUC) to predict binary FFR ≤0.80 (compared using the DeLong method).

Index (AUC)	Pd/Pa (0.86)					
Pd/Pa (0.86)	N/A	iFR (0.84)				
iFR (0.84)	<0.001	N/A	RFR (0.85)			
RFR (0.85)	<0.001	0.1371	N/A	dPR (0.85)		
dPR (0.85)	<0.001	<0.001	0.6464	N/A	CNN (0.88)	
CNN (0.88)	0.0037	<0.001	<0.001	<0.001	N/A	RNN (0.84)
RNN (0.84)	<0.001	0.6375	0.3091	0.2234	<0.001	N/A

AUC: area under the receiver operating characteristic curve; CNN: convolutional neural network; dPR: diastolic pressure ratio; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; N/A: not applicable; Pd/Pa: resting distal coronary pressure to aortic pressure ratio; RFR: relative flow reserve; RNN: recurrent neural network

Supplementary Table 5. Comparison of the potential advantages in design of the ARTIST study with pivotal studies on the prediction of FFR from resting coronary pressure curves.

Study	No. of patients	No. of lesions	Deep learning	Designed to create new index	Focus beyond distal to aortic pressure during a specific period of the cardiac cycle	Potential to identify non-pre-specified qualitative features	Resting index	Accuracy against binary FFR ≤0.80 (%)
ARTIST	1,666	1,718	+	+	+	+	Deep learning-derived algorithm	80%
ADVISE	131	157	-	+	-	-	iFR	88%
Johnson et al JACC 2013	1,129	1,129	-	-	-	-	Pd/Pa iFR	NA
VERIFY [14]	706	706	-	-	-	-	iFR	60%
VERIFY 2 [15]	197	257	-	-	-	-	Pd/Pa iFR	80% 79%
CONTRAST [13]	763	763	-	-	-	-	Pd/Pa iFR	79% 80%
RESOLVE	1,768	1,593	-	-	-	-	Pd/Pa iFR	82% 80%
Van ‘t Veer et al [7]	197	197	-	+	-	-	Several NHPR	76-77%
Matsumura et al [10]	592	592	-	+	+	-	Qualitative parameters in addition to Pd/Pa and iFR	NA
Svanerud et al EuroIntervention 2018	1,137	1,305	-	+	-	-	RFR	81%

Johnson et al EHJ 2019	833	893	-	+	-	-	dPR	NA

dPR: diastolic pressure ratio; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; NHPR: non-hyperaemic pressure ratio; Pd/Pa: resting distal coronary pressure to aortic pressure ratio; RFR: relative flow reserve