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

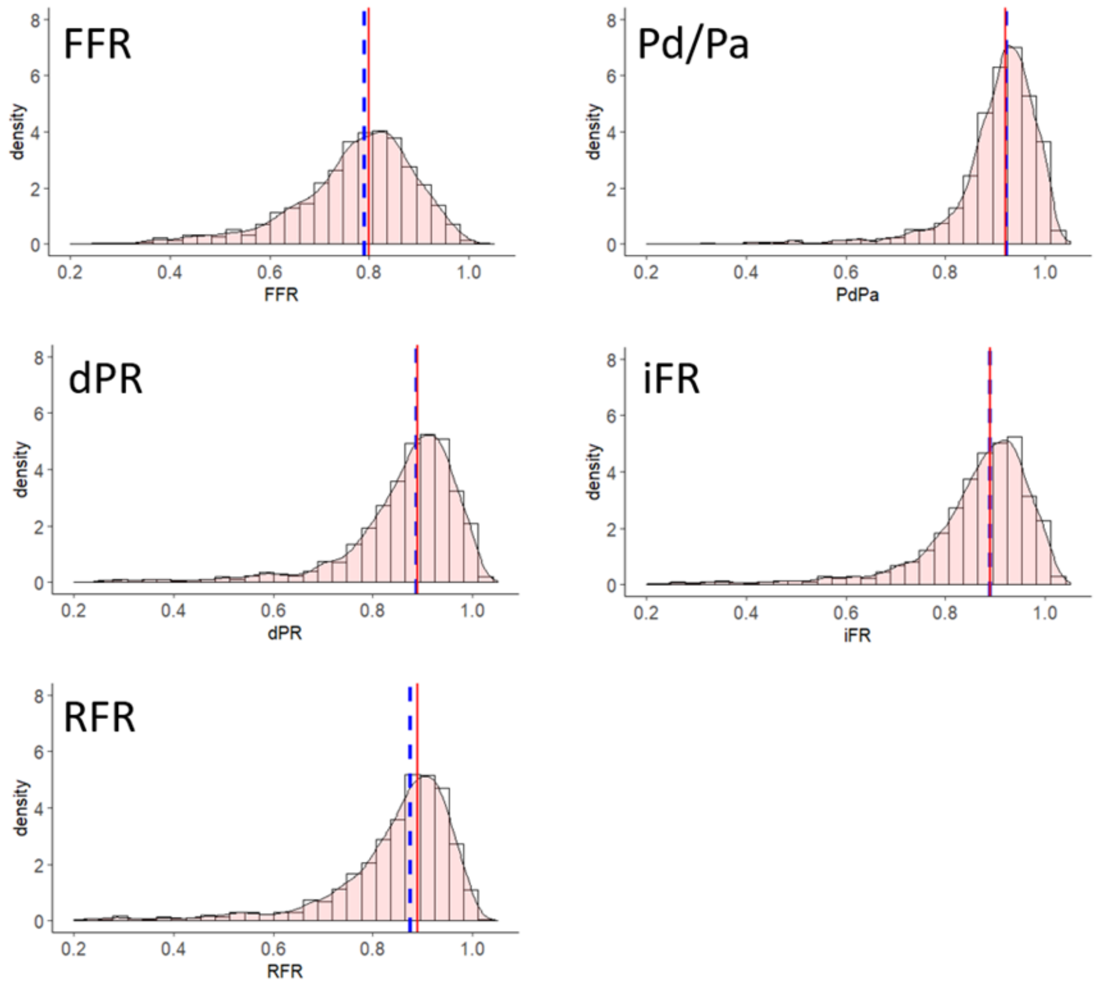
A one-dimensional convolutional neural network (CNN) was used to classify resting pressure recordings into FFR positive (FFR ≤0.80) or FFR negative (FFR >0.80) binary categories, and to predict FFR as a continuous outcome. A CNN can automatically learn and identify features that are present among the 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.

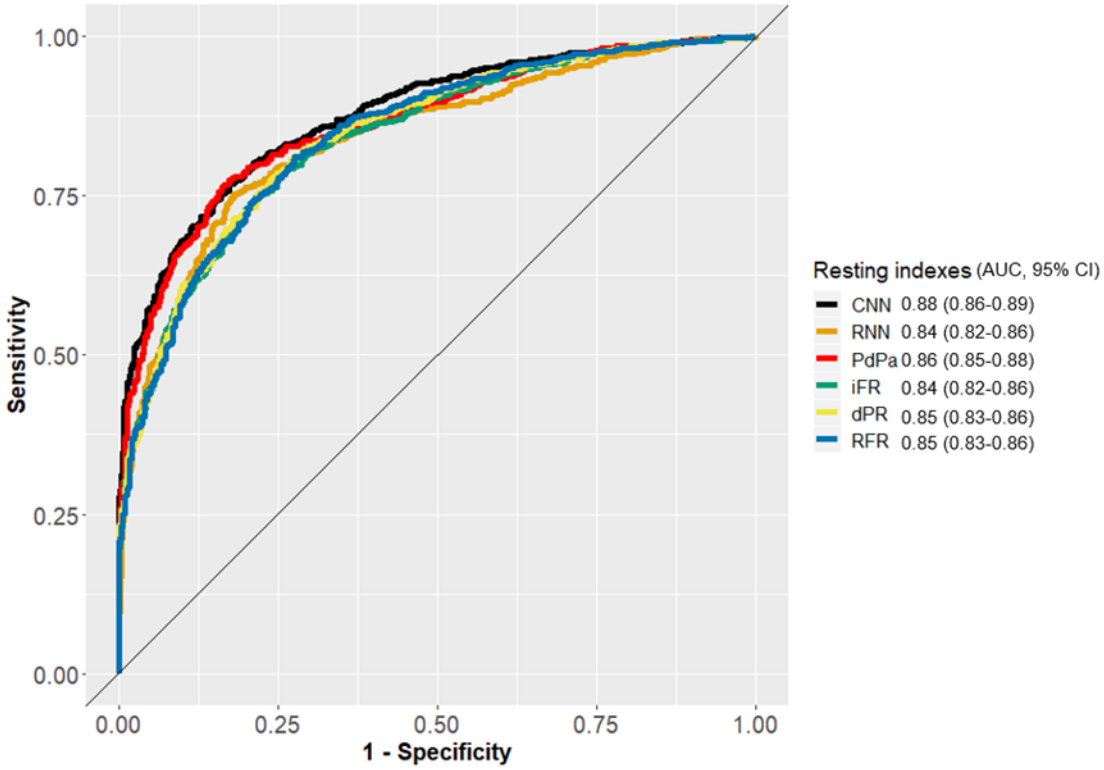
Both CNN and RNN were trained using 4,000 epochs; at each epoch the models were fed in batches of 64. All deep learning models were implemented using scikit-learn in Python™.



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