Supplementary

Appendix 1

Methods

1. CT acquisition and reconstruction

A third-generation dual source CT (SOMATOM Force, Siemens Healthineers) was employed for CT-MPI and CCTA imaging.

The scan range of dynamic CT-MPI will be planned based on the calcium score images to cover the whole left ventricle. Intravenous ATP infusion will be maintained for 3 minutes at 160 μg/kg/min before CT-MPI scan. A bolus of contrast media (50 mL, Iopamidol, 370 mg iodine/mL, Bayer, Germany) will be injected into antecubital vein at the rate of 6 mL/s, followed by a 40 mL saline flush. Dynamic CT-MPI acquisition will be started 4 seconds after the begin of contrast injection. The end-systolic phase (triggered at 250 ms after the R wave in all participants) is set for the dynamic acquisition by using a shuttle mode technique with a coverage of 10.5 cm for complete imaging of the whole left ventricle. Scans will be launched every second or third heart cycle according to participants' heart rate, resulting in a series of 10 to 15 phases acquired over a fixed period of 32 s. The acquisition parameters of dynamic CT-MPI are listed as follow: collimation = 96×0.6 mm^2, CARE kV will be used and the reference tube voltage =80 kVp, rotation time =250 ms, CARE dose 4D will be used and the effective current =300 mAs, reconstructed slice thickness = 3 mm and reconstructed slice interval =2 mm.

A bolus of contrast media (iopamidol 370 mg iodine/mL, Bayer, Germany) will be injected into the antecubital vein at the rate of 4.5–5 mL/s, followed by injection of a 40 mL saline flush, using a dual-barrel power injector (Tyco-Mallinckrodt, US). The amount of contrast media will be determined according to the patient's body weight and the scanning time. Prospective ECG-triggered sequential acquisition will be performed in all participants for CCTA, with triggering window coveting from end-systolic to mid-diastolic phase. The detailed parameters are listed as follow: collimation =96×0.6 mm^2, reconstructed slice thickness =0.75 mm, reconstructed slice interval = 0.5 mm, rotation time =250 ms and application of automated tube voltage and current modulation (CAREKv, CAREDose 4D, Siemens Healthineers, Germany). The reference tube current will be set as 320 mAs and the reference tube voltage will be set as 100 kVp.

2. CT-FFR measurement

As introduced recently, we used a machine-learning based algorithm for CT-FFR simulation (cFFR, version 3.0, Siemens Healthineers). It's an alternative to physics-based approach and can be used on-site to calculate CT-FFR value. It's trained using a synthetically generated database of 12,000 different anatomies of coronary arteries with randomly placed stenosis among different branches and bifurcations. A computational fluid dynamics (CFD) by solving reduced-ordered Navier-Stokes equations is applied to calculate the pressure and flow distribution for each coronary tree. Quantitative features of anatomy and computed CT-FFR value were extracted for each location along the coronary tree. Then deep machine learning model is trained by using a deep neural network with four hidden layers to learn the relationship between the FFR value and quantitative anatomic features.

For the on-site processing, after CCTA data were successfully loaded, the centerline and luminal contours for whole coronary tree were automatically generated. The centerline and luminal contour are fundamental and critical information for computing CT-FFR value. They were manually adjusted when needed. Users then manually identified all stenotic lesions to extract their geometrical features required for cFFR algorithm. Finally, those data were input into the pre-learned model and cFFR was computed automatically at all locations in the coronary arterial tree, and the resulting values were visualized by color-coded 3D coronary maps.

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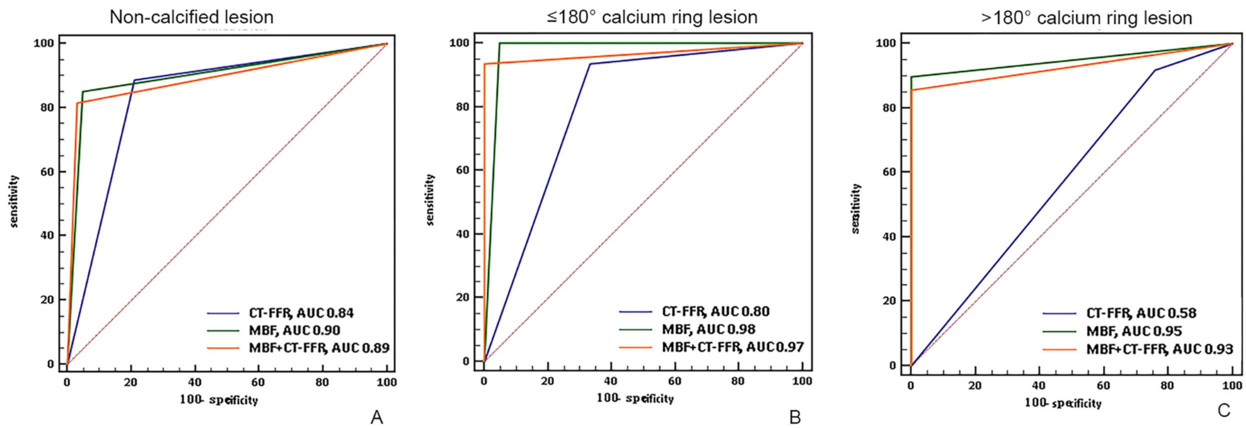

Figure S1 ROC curve analysis of dynamic CT-MPI, CT-FFR and CT-FFR + dynamic CT-MPI for identifying functionally significant coronary stenosis according to calcium morphology with reference to ICA/FFR. (A) For non-calcified lesions, the AUCs of CT-FFR, dynamic CT-MPI and CT-FFR + dynamic CT-MPI were similar between subgroups (all P>0.05). (B) For calcified lesions with calcium arc ≤180°, the AUCs of dynamic CT-MPI and CT-FFR + dynamic CT-MPI were significantly larger than that of CT-FFR (all P<0.01). (C) For calcified lesions with calcium arc >180°, the AUCs of dynamic CT-MPI and CT-FFR + dynamic CT-MPI were significantly larger than that of CT-FFR (all P<0.001). AUC, area under curve; CT, computed tomography; CT-MPI, computed tomography myocardial perfusion imaging; FFR, fractional flow reserve; ICA, invasive coronary angiography; MBF, myocardial blood flow; ROC, receiver operating characteristic.

Table S1 Interobserver reproducibility

	ICC	Kappa	95% CI	P value
Vessel-based CACS	0.997	–	0.994–0.998	<0.001
Diameter stenosis	0.889	–	0.816–0.945	<0.001
Lesion length	0.973	–	0.950–0.986	<0.001
CT-FFR	0.886	–	0.776–0.942	<0.001
MBF	0.971	–	0.945–0.985	<0.001
Calcium morphology	–	0.884	–	<0.001

CACS, coronary artery calcium score; CI, Confidence interval; CT, computed tomography; FFR, fractional flow reserve; ICC, intraclass correlation coefficient; MBF, myocardial blood flow.

Table S2 Intra-observer reproducibility

	ICC	Kappa	95% CI	P value
Vessel-based CACS	0.994		0.998–0.997	<0.001
Diameter stenosis	0.914		0.879–0.947	<0.001
Lesion length	0.986		0.974–0.993	<0.001
CT-FFR	0.939		0.874–0.970	<0.001
MBF	0.985		0.972–0.992	<0.001
Calcium morphology	0.922	0.922	–	<0.001

CACS, coronary artery calcium score; CI, Confidence interval; CT, computed tomography; FFR, fractional flow reserve; ICC, intraclass correlation coefficient; MBF, myocardial blood flow.

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Table S3 Univariable and multivariable analyses of MBF for mismatch with ICA/FFR

Characteristics	Univariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Vessel-based CACS	0.999	0.997–1.001	0.556	1.000	0.997–1.003	0.937
Diameter stenosis	1.181	0.845–1.651	0.329	1.269	0.888–1.814	0.191
Lesion length	1.000	0.971–1.031	0.984	–	–	–
Calcium morphology	0.851	0.452–1.602	0.616	1.290	0.511–3.257	0.590
Number of calcified segments of target vessels	0.682	0.386–1.206	0.189	0.513	0.198–1.327	0.169

CACS, coronary artery calcium score; CI, Confidence interval; FFR, fractional flow reserve; ICA, invasive coronary angiography; MBF, myocardial blood flow.

Table S4 Vessel-based diagnostic performance of CT-FFR and MBF according to vessel-specific CACS

	Q1 (n=57)			Q2 (n=58)			Q3 (n=57)			Q4 (n=57)		
	MBF*	CT-FFR§	P value	MBF	CT-FFR	P value	MBF	CT-FFR	P value	MBF	CT-FFR	P value
Sensitivity	76.9 (10/13) [46.2–95.0]	84.6 (11/13) [54.6–98.1]	1.000	89.5 (17/19) [66.9–98.7]	84.2 (16/19) [60.4–96.6]	1.000	93.1 (27/29) [77.2–99.2]	93.1 (27/29) [77.2–99.2]	1.000	93.5 (29/31) [78.6–99.2]	96.8 (30/31) [83.3–99.9]	1.000
Specificity	97.7 (43/44) [88.0–99.9]	81.8 (36/44) [67.3–91.8]	0.016	92.3 (36/39) [79.1–98.4]	59.0 (23/39) [42.1–74.4]	0.002	100 (28/28) [87.7–100.0]	57.1 (16/28) [37.2–75.5]	<0.001	96.2 (25/26) [80.4–99.9]	38.5 (10/26) [20.2–59.4]	<0.001
NPV	93.5 (43/46) [84.2–97.5]	94.7 (36/38) [83.3–98.5]	1.000	94.7 (36/38) [82.9–98.5]	88.5 (23/26) [72.4–95.7]	0.389	93.3 (28/30) [78.6–98.2]	88.9 (16/18) [66.9–96.9]	0.624	92.6 (25/27) [76.6–98.0]	90.9 (10/11) [57.8–98.7]	1.000
PPV	90.9 (10/11) [58.5–98.6]	57.9 (11/19) [41.3–72.8]	0.100	85.0 (17/20) [65.4–94.4]	50.0 (16/32) [39.6–60.4]	0.011	100 (27/27) –	69.2 (27/39) [59.2–77.7]	0.001	96.7 (29/30) [80.9–99.5]	65.2 (30/46) [57.8–71.9]	0.001
Accuracy	93.0 (53/57) [83.0–98.1]	82.5 (47/57) [70.1–91.3]	0.008	91.4 (53/58) [81.0–97.1]	67.2 (39/58) [53.7–79.0]	0.012	96.5 (55/57) [87.9–99.6]	75.4 (43/57) [62.2–85.9]	0.002	94.7 (54/57) [85.4–98.9]	70.1 (40/57) [56.6–81.6]	<0.001

Group by quartile. *, MBF cut-off value = 99 mL/100 mL/min; §, CT-FFR cut-off value = 0.78. CT, computed tomography; FFR, fractional flow reserve; MBF, myocardial blood flow; CACS, coronary artery calcium score; NPV, negative predictive value; PPV, positive predictive value.

Table S5 Patient-based diagnostic performance of CT-FFR and MBF according to CAD-RADS grade

	CAD-RADS 2 and 3 (n=60)			CAD-RADS 4 (n=120)		
	MBF*	CT-FFR§	P value	MBF	CT-FFR	P value
Sensitivity	87.5 (7/8) [47.4–99.7]	75.0 (6/8) [34.9–96.8]	1.000	90.0 (63/70) [80.5–95.9]	88.6 (62/70) [78.7–94.93]	1.000
Specificity	100 (52/52) [93.2–100]	78.8 (41/52) [65.3–88.9]	<0.001	94.0 (47/50) [83.5–98.8]	58.0 (29/50) [43.2–71.8]	<0.001
NPV	98.1 (52/53) [89.3–99.7]	95.3 (41/43) [86.0–98.6]	0.585	87.0 (47/54) [76.8–93.2]	78.4 (29/37) [64.4–87.9]	0.274
PPV	100 (7/7) –	35.3 (6/17) [22.0–51.3]	0.006	95.5 (63/66) [87.5–98.4]	74.7 (62/83) [67.8–80.5]	0.001
Accuracy	98.3 (59/60) [91.1–100]	78.3 (47/60) [65.8–87.9]	<0.001	91.7 (110/120) [85.2–95.9]	75.8 (91/120) [67.2–83.2]	<0.001

*, MBF cut-off value = 99 mL/100 mL/min; §, CT-FFR cut-off value = 0.76. CAD-RADS, Coronary Artery Disease–Reporting and Data System; CT, computed tomography; FFR, fractional flow reserve; MBF, myocardial blood flow; CACS, coronary artery calcium score; NPV, negative predictive value; PPV, positive predictive value.

