## 1. CCTA + dynamic CT-MPI group

Patients will be asked to refrain from intake of β-blocker or caffeine for 24 hours and to maintain fast for 4 hours before the scan.

### *CCTA + Dynamic CT-MPI protocol*

A third generation dual-source CT (SOMATOM Force, Siemens Healthcare, Forchheim, Germany) will be employed for CCTA and dynamic CT-MPI acquisition. Calcium score will be firstly performed to calculate the calcification burden of each epicardial vessels. 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, reconstructed slice thickness = 0.75 mm, reconstructed slice interval = 0.5mm, 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.

On-site evaluation will be performed by a cardiovascular radiologist to interpret CCTA findings. Dynamic CT-MPI will be subsequently performed if CCTA revealed at least one lesion with stenosis extent from 30% to 90% on any major epicardial vessel (diameter ≥ 2mm). Otherwise, patients will be managed following the study paradigm (*Figure 1*) without undergoing dynamic CT-MPI.

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 (50ml, 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, 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.

### *CCTA and dynamic CT-MPI image reconstruction and analysis*

CCTA images will be reconstructed using a medium soft convolution kernel (Bv40) and iterative reconstruction (ADMIRE, level 3). The best systolic as well as best diastolic images will be transferred to an offline workstation (SyngoVia, version VB20A, Siemens Healthineers, Germany) for further analyses.

The diameter stenosis will be calculated as (reference diameter – minimal lumen diameter) / reference diameter and will be measured manually with a digital caliper at the narrowest level of the lesion and the proximal reference on the cross-sectional images. A stenosis grade of 50% or greater in an epicardial vessel with diameter ≥ 2mm on CCTA will be considered to indicate presence of obstructive CAD.

The CT-MPI images will be reconstructed using a dedicated kernel for reduction of iodine beam-hardening artifacts (Qr36) and analyzed using a CT-MPI software package (VPCT, SyngoVia, version VB20A, Siemens Healthineers, Germany). Motion correction will be applied in necessary cases to correct for breathing-related mis-registration of the left ventricle. For quantification of myocardial blood flow (MBF), the influx of contrast medium will be measured using the arterial input function (AIF). The AIF will be sampled in the descending aorta by including both the cranial and caudal sections. For quantification of the MBF, the myocardial time attenuation curves will be coupled with the AIF using a hybrid deconvolution model. For quantitative analysis, the region of interest (ROI) will be drawn to cover the whole area of suspected perfusion defect within the segment or cover the whole segment when perfusion defect will be absent. The stenosis-subtended territories and reference territories will be each determined according to the fusion images of coronary vasculature and perfusion map. The mean value of stress MBF will be measured for each segment of both stenosis-subtended territories and reference territories.


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According to the previous study, the absolute MBF value <100 mL/100mL/min will be considered as the presence of myocardial ischemia [7].

## 2. CCTA + CT-FFR group

CCTA acquisition settings will be identical to the CCTA protocol used in CCTA + CT-MPI group.

### *Image reconstruction and analysis*

CCTA images will be reconstructed using a medium soft convolution kernel (Bv40) and iterative reconstruction (ADMIRE, level 3). The best systolic as well as best diastolic images will be transferred to an offline workstation (SyngoVia, version VB20A, Siemens Healthineers, Germany) for further analyses.

Lesion-specific CT-FFR values will be measured for all stenosis with diameter stenosis ≥30% on any epicardial vessel with diameter ≥2 mm. The current study employs a machine learning (ML)-based approach for CT-FFR simulation (cFFR, version 3.0, Siemens Healthineers, Germany). This model will be trained on a large database of synthesized coronary anatomies, where the reference values are computed by using a computational fluid dynamics based model. For the on-site processing, after CCTA data is successfully loaded, the centerline and luminal contours for whole coronary tree are automatically generated. The centerline and luminal contour are fundamental and critical information for computing CT-FFR value. They are manually adjusted when needed. Users then manually identify all stenotic lesions to extract their geometrical features required for cFFR algorithm. Finally, those data are input into the pre-learned model and cFFR is computed automatically at all locations in the coronary arterial tree, and the resulting values are visualized by color-coded 3D coronary maps. The lesion-specific CT-FFR values are measured at the distal shoulder of the lesion, where no plaque can be detected. Downstream treatment strategy will be decided based on the results of CT-FFR (*Figure 1*).


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