Study Protocol

Official Title	Functional ComprEhensive AssessmenT by Intravascular UltrasoUnd Reconstruction in Patients With Suspected IschEmic Coronary Artery Disease (FEATURE)
NCT Number	NCT05694065
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Principal Investigator	Fenghua Ding
Responsible Party	Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

1. Study Background

Intravascular ultrasound (IVUS), an invasive coronary imaging technique, provides accurate visualization of lumen dimensions and subintimal plaque morphology. This facilitates guiding percutaneous coronary intervention (PCI), intra-procedural stent sizing optimization and post-procedural stent apposition assessment in patients with ischemic heart disease[1].

Although IVUS-derived minimal lumen area (MLA) could predict functionally significant stenosis, defined by fractional flow reserve (FFR)⩽0.80 - the gold standard for functional evaluation of coronary stenosisI[2-3], its diagnostic performance varies: MLA cutoff values (2.0 - 4.0 mm^2) showed moderate accuracy (60-80%) for non-left main lesions[4-7] with variation observed across coronary vessel segments[8]; A recent study reported that MLA<2.79 mm^2 achieved 77.4% accuracy (AUC=0.86) with sensitivity of 76.2% and specificity of 78.5% in large vessels (diameter >2.5mm by visual estimation)[9]. Despite providing valuable anatomical insights, IVUS remains suboptimal for physiological ischemia assessment. However, a recent landmark trial demonstrated comparable major adverse cardiac events rates between IVUS-guided PCI and FFR-guided PCI, while the latter significantly reduced stent utilization[10].

The complementary nature of these two modalities presents a compelling rationale for their integrated use. Notably, the recent development of an artificial intelligence-enhanced computational ultrasonic flow ratio (UFR), enables derivation of functional information directly from IVUS datasets. This innovation establishes a unified morpho-functional assessment system, effectively obviating dependence on pressure-wire instruments and pharmacologically-induced hyperemia[11]. Preliminary data showed 92% diagnostic concordance between UFR and FFR (AUC=0.97)[12], though evidence remains limited to retrospective, single-vessel analyses.

This prospective, single-center observational study will consecutively enroll patients with suspected ischemic heart disease to evaluate the diagnostic performance of catheterization laboratory-derived UFR in identifying hemodynamically significant coronary stenosis (defined as FFR ≤0.80).

2. Study Objective

Investigating the diagnostic accuracy of online UFR assessment to identify hemodynamically significant coronary stenosis in patients with suspected ischemic heart disease using angiography-derived FFR as a reference standard.

2.1 Primary Endpoint

Diagnostic accuracy of online UFR as compared with FFR to identify hemodynamically significant coronary stenosis (FFR ≤0.80).

2.2 Second Endpoint

Sensitivity and specificity of online UFR as compared with IVUS-derived MLA, when using FFR as a golden standard.

2.3 Prespecified Subgroup Analysis

Lesion location, multivessel disease and imaging catheters.

3. Study Design

3.1 Study Description

This is a prospective, single-center, observational clinical study. Patients with suspected ischemic heart disease admitted for coronary angiography will be consecutively enrolled.

3.2 Study Subject

3.2.1 Inclusion Criteria

1. Subject must be ≥ 18 years
2. Patients suspected with ischemic heart disease
3. ≥ 1 diseased vessel with angiographic percent diameter stenosis between 40% and 80% in a vessel ≥ 2.5mm by visual estimation
4. Target vessels are limited to major epicardial coronary arteries (left anterior descending artery [LAD], left circumflex artery [LCX], right coronary artery [RCA])

3.2.2 Exclusion Criteria

1. Patients with previous coronary artery bypass grafting (CABG)
2. Myocardial infarction within 72h of coronary angiography

3. Allergy to the contrast agent or adenosine

4. Left main coronary artery stenosis ≥ 50%

5. Target vessel with in-stent restenosis

6. Target vessel with severe tortuosity or angulation

7. 100% occlusion of target vessel

8. Target vessel spasm or injury

9. Target vessel with severe myocardial bridge

10. Target vessel with severe thrombosis

11.IVUS pullback fails to cover the complete target lesion

12. Presence of false lumen at target vessel based on IVUS

13. A serum creatinine level >150 umol/l, or a glomerular filtration rate < 45 ml/kg/1.73 m^2

14. Heart failure

15. Ineligible for diagnostic intervention (IVUS or FFR examination)

3.3 Sample Size Calculation

Study population and sample size calculation are based on the diagnostic performance of previous studies, where an accuracy of 92% was found for UFR. Investigators conservatively estimate the diagnostic accuracy of online UFR assessment as 90% for consecutively enrolled patient population, and with a test target value set as 78% at a two-side significance level of 0.05, statistical power as 90%. Considering incomplete FFR/UFR data of 10% at most, a total of 112 patients need to be enrolled.

4. Data Acquisition

FFR is measured using a pressure wire (St. Jude Medical, Saint Paul, MN, USA) or a pressure microcatheter (TruePhysio, Insight Lifetech, Shenzhen, China) at least 2 cm distal to the most distal part of the target lesion. FFR is calculated as the ratio between the average distal pressure and the average aortic pressure recorded during stable maximal hyperemia induced by injection of adenosine via an antecubital vein at 140~180 μg/ (kg·min).

IVUS images are obtained after intracoronary injection of nitroglycerin using either OptiCross 40 MHz or OptiCross HD 60 MHz Imaging Catheter with an automated pullback at a speed of 1 mm/s and a frame rate of 30 frames/s on the commercially available systems (OptiCross, iLab(TM) Polaris, Boston Scientific, Boston, USA). IVUS catheters should be consistent with the FFR pressure guide wire measurement. After IVUS image acquisition, the image pullbacks will be transferred to computation of UFR online using commercially available software (IvusPlus, version V1; Pulse Medical, Shanghai, China) by a certified analyst who is blinded to the FFR data. The algorithm of UFR computation includes the reconstruction of the geometric model and computation of the pressure drop along the imaged segment. Firstly, the arterial lumen and external elastic membrane contours are automatically delineated and reconstructed in 3D by AI. Secondly, the ostia of side branches perpendicular to the side branch centerline are automatically reconstructed to enable cross-sectional area measurement of the side branches. Subsequently, the reference vessel diameter (RVD), the hypothetical healthy lumen with absence of any stenosis, is derived based on the bifurcation fractal law. Finally, the pressure drops along each cross-section of the pullback are calculated using validated computational FFR algorithm based on fluid dynamics equations, and the UFR pullback will be obtained.

5. Statistical Analysis

Continuous variables are reported as mean±standard deviation (SD) for normally distributed data or median (interquartile range [IQR]) for non-normally distributions. Categorical variables are expressed as counts (percentages). The median value of FFR and UFR are compared by Wilcoxon signed-rank test. Correlation between FFR and UFR is assessed by the Spearman or Pearson correlation analysis, as appropriate. Bland-Altman analysis quantifies measurements bias and 95% limits of agreement between FFR and UFR. The diagnostic discrimination abilities of UFR and MLA are compared by the area under the receiver operating characteristic (ROC) curves using the DeLong method. Cutoff value of $\leqslant$0.80 is used for FFR and UFR to define the physiological significance of a coronary stenosis. All statistical analyses are performed using R v4.5.0, (R Foundation for Statistical Computing, Vienna, Austria.)

and MedCalc v23.2.1 (MedCalc Software, Ostend, Belgium), with two-sided $P<0.05$ considered statistically significant.

6. References

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