Predictive value of coronary artery computed tomography-derived fractional flow reserve for cardiovascular events in patients with coronary artery disease

Hongwei Han  
Department of Cardiovascular Medicine, 903 RD Hospital of PLA

Meijun Liu  
Department of Cardiovascular Medicine, Hangzhou First People's Hospital

Yang Yu  
Department of Cardiovascular Medicine, 903 RD Hospital of PLA

Yuan Chen  
Department of Cardiovascular Medicine, 903 RD Hospital of PLA

Yizhou Xu (✉️ 929600580@qq.com)  
Department of Cardiovascular Medicine, Hangzhou First People's Hospital

Research Article

Keywords: coronary CT-derived fractional flow reserve, FFR-CT, coronary arteriosclerosis, atherosclerotic heart disease, cardiovascular events, predictive value

Posted Date: March 17th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2682752/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: Coronary computed tomography-derived fractional flow reserve (FFR-CT) assesses whether coronary artery lesions will result in myocardial ischemia.

Aim: This study aimed to evaluate the predictive value of FFR-CT for cardiovascular events in patients with coronary artery disease (CAD).

Methods: Data were collected retrospectively from patients with CAD who underwent FFR-CT at our hospital from January 2020 to February 2022 (1-year average follow-up). Patients were divided into ischemic (FFR-CT ≤ 0.80) and non-ischemic (FFR-CT > 0.80) groups. The incidence of endpoint events (cardiac death, acute myocardial infarction, unplanned revascularization, unstable angina, and stable angina) was calculated. The FFR-CT value was correlated with endpoint events using Cox regression models and Kaplan-Meier survival curves.

Results: We recruited 134 patients (93 [69.4%] and 41 [30.6%] patients in the ischemic and non-ischemic groups, respectively). Compared to the non-ischemic group, the ischemic group had a higher proportion of men, patients with type 2 diabetes and hypertension, and patients taking antiplatelet drugs and β-blockers (all \(P < 0.05\)). Other parameters were comparable. Multivariate Cox regression analysis revealed no significant differences between the groups for cardiac death, acute myocardial infarction, unplanned revascularization, and unstable angina; the incidence of stable angina events (HR=3.092, 95% CI: 1.362–7.022, \(P = 0.007\)) was significantly higher in the ischemic group. Kaplan-Meier survival analysis identified a significant difference in event-free survival for stable angina between the groups (\(P = 0.002\)).

Conclusion: FFR-CT showed an independent predictive value for stable angina within 1 year of examination in patients with CAD.

1 Introduction

Measurement of coronary computed tomography-derived fractional flow reserve (FFR-CT) is one of the newest technologies to assess whether coronary artery lesions will result in myocardial ischemia. FFR-CT combines the benefits of functional and anatomical assessments, and this non-invasive imaging examination can significantly lower medical expenses. Thus, FFR-CT has emerged as an area of interest in the cardiovascular field. Relevant clinical studies have recently attested to FFR-CT technology's reliability and safety (1–3). In this article, we aimed to investigate the predictive value of FFR-CT for cardiovascular events in patients with coronary artery disease (CAD).

2 Materials And Methods

2.1 Patients
This was a single-center, retrospective, non-randomized study of 134 patients who underwent FFR-CT in the inpatient and outpatient departments of 903 RD Hospital of PLA, and Hangzhou First People's Hospital in China from January 2020 to February 2022. Patients were separated into ischemic (FFR-CT ≤ 0.80) and non-ischemic (FFR-CT > 0.80) groups. The inclusion criteria were as follows: (i) age over 18 years; (ii) coronary computed tomography angiography (CTA) examination revealing no occlusive vessel lesions; (iii) diagnosed with CAD; and (iv) the presence of clear, legible coronary CTA images free of artifacts, noise, or other signs of poor quality. The exclusion criteria were as follows: (i) patients with a history of percutaneous coronary intervention (PCI); (ii) patients with a history of mechanical or biological artificial heart valve or cardiac pacemaker implantation; (iii) patients with a history of coronary artery bypass grafting (CABG); (iv) patients who experienced acute myocardial infarction within the 30 days prior to the FFR-CT examination; (v) patients with any serious life-threatening complications, including complex congenital heart disease and severe arrhythmia; (vi) patients with other diseases with chest pain symptoms, such as cardiomyopathy and severe heart valve diseases; (vii) patients with cancer-related cachexia; and (viii) patients who had undergone major surgery within 6 months of the screening. The study was approved by the Ethics Committee of Hangzhou First People's Hospital, approval number: IIT-20221111-0176-01. All patients provided written informed consent for participation.

2.2 Model-based analysis of FFR-CT

FFR-CT measurement software was provided by Shenzhen RaySight Intelligent Medical Technology Co., Ltd. (China). The software used coronary CTA images to automatically create a 3D model of the coronary artery, accurately map out the blood vessels, collect pertinent information like coronary artery pressure, coronary artery flow at maximum hyperemia, and microcirculation resistance; corresponding mathematical models were then produced. The pressure and velocity of each coronary artery grid point in the 3D model were calculated by the solver to determine the FFR-CT value (4–6).

2.3 Assessment criteria for myocardial ischemia

Myocardial ischemia was diagnosed with FFR-CT measurements ≤ 0.8. FFR-CT measurements > 0.8 indicated that 90% of the coronary artery lesions would not induce myocardial ischemia; 0.75 < FFR-CT ≤ 0.80, the so-called “grey area” in clinical practice, indicated that the treatment strategy had to be evaluated thoroughly based on clinical circumstances; FFR-CT ≤ 0.75 indicated that coronary artery lesions could induce myocardial ischemia, and interventional therapy was typically advised.

2.4 Clinical baseline data collection and follow-up endpoints

Baseline clinical data, such as general information and medications were gathered from patients using patient self-reports, telephone questionnaires, and medical records. General clinical data comprised
demographic characteristics including age, sex, body mass index (BMI); estimated glomerular filtration rate (eGFR); risk factors including smoking history; medical history including hypertension, diabetes, hyperlipidemia, chronic heart failure, atrial fibrillation, and ventricular tachycardia; medications including antiplatelet drugs, anticoagulants, antihyperlipidemic agents, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), β-blockers, coronary vasodilators, hypoglycemic drugs, and diuretics; and family history of CAD. The endpoint events included cardiac death, acute myocardial infarction, unplanned revascularization, unstable angina, and stable angina.

2.5 Statistical methods

Statistical analysis was performed using SPSS software (version 26.0). The measurement data with normal distribution are expressed as $\bar{x} \pm s$ (mean ± standard deviation), and the independent sample t-test was used for comparison between groups. Count data are expressed as cases (%), and the chi-square test was used for comparison between groups. The incidence of endpoint events was calculated in both groups, and the event-free survival rates were estimated using Kaplan-Meier survival curves. The correlation between FFR-CT and endpoint events was analyzed using Cox regression models, and the statistically and clinically significant variables at baseline were corrected using a multivariate analysis. All data analysis implemented two-sided testing, and the differences were considered statistically significant when $P<0.05$.

3 Results

3.1 Comparison of clinical baseline information

The study involved 134 patients overall, with 40 women and 94 men (79.1% and 29.9%, respectively). There were 93 patients (69.4%) in the FFR-CT $\leq 0.80$ group and 41 patients (30.6%) in the FFR-CT $>0.80$ group. No significant differences in age; BMI; eGFR; smoking history; hyperlipidemia; atrial fibrillation; chronic heart failure; ventricular tachycardia; use of antihyperlipidemic agents, anticoagulants, ACEI/ARBs, coronary vasodilators, hypoglycemic drugs, and diuretics; or family history of CAD were observed between the two groups (all $P>0.05$). Compared to the FFR-CT $>0.80$ group, the proportion of men in the FFR-CT $\leq 0.80$ group was higher, as were the proportions of patients with type 2 diabetes, hypertension, and the use of β-blockers and antiplatelet medications (all $P<0.05$). The baseline data of the patients in the FFR-CT $\leq 0.80$ and FFR-CT $>0.80$ groups are compared in Table 1.
### Table 1
Comparison of clinical baseline information of participants in FFR-CT ≤ 0.80 group and FFR-CT > 0.80 group

<table>
<thead>
<tr>
<th></th>
<th>FFR-CT &gt; 0.80 (n = 41)</th>
<th>FFR-CT ≤ 0.80 (n = 93)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, x ± s)</td>
<td>54 ± 13</td>
<td>63 ± 12</td>
<td>0.775</td>
</tr>
<tr>
<td>Men [Cases (%)]</td>
<td>23 (17.2%)</td>
<td>71 (53.0%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Women [Cases (%)]</td>
<td>18 (13.4%)</td>
<td>22 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>BMI value (kg/m², x ± s)</td>
<td>23.9 ± 2.9</td>
<td>23.6 ± 1.9</td>
<td>0.685</td>
</tr>
<tr>
<td>eGFR [ml·min⁻¹·1.73m⁻²]</td>
<td>95.0 ± 7.9</td>
<td>94 ± 5.5</td>
<td>0.867</td>
</tr>
<tr>
<td>Smoking history [Cases (%)]</td>
<td>18 (13.4%)</td>
<td>39 (29.1%)</td>
<td>0.832</td>
</tr>
<tr>
<td>Medical history [Cases (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>14 (10.4%)</td>
<td>50 (37.3%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (14.9%)</td>
<td>66 (49.3%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7 (5.2%)</td>
<td>28 (20.9%)</td>
<td>0.113</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (4.5%)</td>
<td>21 (15.7%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>7 (5.2%)</td>
<td>11 (8.2%)</td>
<td>0.412</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>6 (4.5%)</td>
<td>9 (6.7%)</td>
<td>0.402</td>
</tr>
<tr>
<td>Combined drugs [Cases (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>22 (16.4%)</td>
<td>68 (50.7%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>5 (3.7%)</td>
<td>16 (11.9%)</td>
<td>0.462</td>
</tr>
<tr>
<td>Antihyperlipidemic agents</td>
<td>21 (15.7%)</td>
<td>62 (46.3%)</td>
<td>0.090</td>
</tr>
<tr>
<td>ACEI/ARBs</td>
<td>22 (16.4%)</td>
<td>59 (44.0%)</td>
<td>0.286</td>
</tr>
<tr>
<td>β-blockers</td>
<td>15 (11.2%)</td>
<td>55 (41.0%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Coronary vasodilators</td>
<td>5 (3.7%)</td>
<td>21 (15.7%)</td>
<td>0.161</td>
</tr>
<tr>
<td>Hypoglycemic drugs</td>
<td>14 (10.4%)</td>
<td>42 (31.3%)</td>
<td>0.234</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; FFR-CT, coronary computed tomography-derived fractional flow reserve.
<table>
<thead>
<tr>
<th></th>
<th>FFR-CT &gt; 0.80 (n = 41)</th>
<th>FFR-CT ≤ 0.80 (n = 93)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>13 (9.7%)</td>
<td>25 (18.7%)</td>
<td>0.568</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>5 (3.7%)</td>
<td>15 (11.2%)</td>
<td>0.556</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; FFR-CT, coronary computed tomography-derived fractional flow reserve.

3.2 Comparison of clinical outcomes

The average follow-up period of the study was 1 year. There were seven patients with cardiac death, including four in the FFR-CT ≤ 0.80 group and three in the FFR-CT > 0.80 group; there were nine patients with acute myocardial infarction, including seven in the FFR-CT ≤ 0.80 group and two in the FFR-CT > 0.80 group. Of the 27 patients with unplanned revascularization, 18 were in the FFR-CT ≤ 0.80 group and nine in the FFR-CT > 0.80 group. There were six patients with unstable angina, including four in the FFR-CT ≤ 0.80 group and two in the FFR-CT > 0.80 group. There were 53 patients with stable angina, including 43 in the FFR-CT ≤ 0.80 group and 10 in the FFR-CT > 0.80 group.

Multivariate Cox regression model analysis results revealed that the differences were not statistically significant between the FFR-CT ≤ 0.80 and FFR-CT > 0.80 groups in terms of cardiac death (HR = 0.824, 95% CI: 0.050–13.696, P = 0.893), acute myocardial infarction (HR = 0.688, 95% CI: 0.075–6.275, P = 0.740), unplanned revascularization events (HR = 0.737, 95% CI: 0.231–2.346, P = 0.605), and unstable angina events (HR = 0.222, 95% CI: 0.001–56.266, P = 0.594). The difference was statistically significant regarding stable angina (HR = 3.092, 95% CI: 1.362–7.022, P = 0.007). Table 2 shows Cox regression analysis of the two groups. Kaplan-Meier survival analysis showed that there was a statistically significant difference in the event-free survival rates for the endpoint of stable angina between the FFR-CT ≤ 0.80 and FFR-CT > 0.80 groups (P = 0.002 on the log-rank test). Figure 1 displays the findings from the Kaplan-Meier survival analysis curves of the two groups.
Table 2
Cox regression analysis of the incidence of endpoint events in the FFR-CT > 0.80 group and FFR-CT ≤ 0.80 group [cases (%)]

<table>
<thead>
<tr>
<th>Endpoint events</th>
<th>FFR-CT &gt; 0.80 (n = 41)</th>
<th>FFR-CT ≤ 0.80 (n = 9)</th>
<th>Univariate Cox regression analysis</th>
<th>Multivariate Cox regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P value</td>
<td>Adjusted HR value a</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>3 (2.24%)</td>
<td>4 (2.99%)</td>
<td>0.929</td>
<td>0.824</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2 (1.49%)</td>
<td>7 (5.22%)</td>
<td>0.216</td>
<td>0.688</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>9 (6.72%)</td>
<td>18 (13.43%)</td>
<td>0.231</td>
<td>0.737</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>2 (1.49%)</td>
<td>4 (2.99%)</td>
<td>0.745</td>
<td>0.222</td>
</tr>
<tr>
<td>Stable angina</td>
<td>10 (7.46%)</td>
<td>43 (30.09%)</td>
<td>0.002</td>
<td>3.092</td>
</tr>
</tbody>
</table>

a: the adjustment factors include age, sex, body mass index (BMI), smoking history, type 2 diabetes, hypertension, hyperlipidemia, chronic heart failure, atrial fibrillation, and combined drugs. FFR-CT, coronary computed tomography-derived fractional flow reserve

4 Discussion

Coronary angiography and intravascular ultrasound (IVUS) can assess the degree of coronary stenosis and type of plaque, and are used to evaluate the diagnostic criteria for CAD. However, it is challenging to use them to assess the functional impact of stenosis on distal blood flow. Failure to recognize the lesion causing myocardial ischemia in a patient may result in untreated vessels that need intervention and overtreated vessels that do not. FFR of coronary arteries has become a recognized indicator that determines the severity of myocardial ischemia. However, FFR is rarely used in clinical practice owing to the high cost and associated surgical risks. By contrast, FFR-CT is a non-invasive examination and shows much promise for future clinical diagnosis and treatment. FFR-CT is currently the newest technology to determine whether coronary artery lesions contribute to myocardial ischemia. In the field of cardiovascular medicine, FFR-CT has emerged as a point of interest because it combines the benefits of anatomical and functional assessments.

This study aimed to evaluate the predictive value of FFR-CT for cardiovascular events in patients with CAD. Multivariate analysis revealed that the incidence of stable angina events was significantly higher in the ischemic group. Kaplan-Meier survival analysis identified a significant difference in event-free survival for stable angina between the groups. Compared to the non-ischemic group, the ischemic group had a
higher proportion of men, patients with type 2 diabetes and hypertension, and patients taking antiplatelet drugs and β-blockers. Hypertension and type 2 diabetes can cause cardiac circulation disorders. In addition to causing vascular endothelial inflammation and altering the structure and function of the vascular endothelium, hypertension and hyperglycemia can also hasten the onset and progression of coronary arteriosclerosis and impact coronary circulation. In addition, when the coronary circulation is obstructed, the coronary vessel structure is remodeled and the diameter reduced, thereby increasing resistance of the circulation vessels and limiting maximum blood flow to the myocardium (9).

According to multivariate Cox regression analysis, there were no significant differences between the FFR-CT ≤ 0.80 and FFR-CT > 0.80 groups for the events of cardiac death, acute myocardial infarction, unplanned revascularization, and unstable angina during the average follow-up period of one year; however, there was a significant difference for stable angina. The Kaplan-Meier survival analysis revealed a significant difference between the FFR-CT ≤ 0.80 and FFR-CT > 0.80 groups in the event-free survival rate for the stable angina endpoint. Our findings indicate that in patients with CAD, the FFR-CT has a good predictive value for the development of stable angina within a year of the examination. This predictive value is independent of baseline characteristics, comorbidities, medications, and other individual factors, suggesting that FFR-CT technology can help clinicians make more accurate assessments of cardiovascular diseases, guide them through more informed treatment decisions, and provide a more accurate prognosis for patients with CAD.

FFR-CT ≤ 0.80 is a good predictor of major cardiovascular events and the need for revascularization. Use of this assessment can reduce unnecessary coronary angiography, according to the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) study (10). As a practical and safe examination, FFR-CT can reduce unnecessary angiography and revascularization and lower the cost of diagnosis and treatment, according to the PLATFORM study (Prospective LongitudinAl Trial of FFRct: Outcome and Resource Impacts) (11). The findings of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study (12) also demonstrated that people with FFR-CT > 0.80 have a lower likelihood of cardiovascular adverse events than people with FFR-CT ≤ 0.80 and that FFR-CT decreased unnecessary coronary interventions. The Syntax III Revolution trial (13) investigated whether FFR-CT would influence clinical decision-making in people with known left main artery lesions or three-branch lesions, in addition to determining whether it would influence interventional strategies. Their findings suggested that FFR-CT changed the revascularization strategies in 12% of people and highlighted that FFR-CT can be used to guide revascularization decisions in people with both lesion types.

In this study, eight patients (5.97%) with cardiovascular events had an FFR-CT of > 0.80, while 18 (13.43%) with no cardiovascular events had an FFR-CT ≤ 0.80. These contradictory findings were attributed to abnormalities of the coronary microcirculation, myocardial hypertrophy, collateral circulation, persistent coronary artery spasm, vascular endothelial dysfunction (14), and other factors in some patients.
The FFR-CT technology currently still has some drawbacks: (i) Accuracy of the FFR-CT calculation is primarily dependent on the quality of the CT images and the patient's physical condition. For instance, accuracy of the FFR-CT is affected by tachycardia, arrhythmia, respiratory artifact, image quality, microcirculation disturbance, prior CABG, and other conditions (15). (ii) There are not many large-scale clinical studies currently investigating FFR-CT. People experiencing acute coronary syndrome have been infrequently recruited to prior studies of FFR-CT, which were typically conducted on people with stable or suspected CAD. Related research demonstrated that FFR-CT may be less accurate as a diagnostic tool due to potential changes in myocardial mass brought on by myocardial infarction (16). As a result, it is unclear whether FFR-CT is beneficial for patients with acute coronary syndrome. (iii) FFR-CT has been used infrequently to assess patients after coronary stent implantation or CABG; this limits the use of this technique for this population. (iv) The semi-automatic differentiation of source data when generating the FFR-CT model could prevent the identification of small-bore vessels with stenosis or occluded branch vessels.

The following are some of the study's limitations: (i) With only a few follow-up cases of acute myocardial infarction, cardiac death, and unstable angina in this study, the results may be biased; (ii) The sample size was small, including only 134 cases; and (iii) This was a single-center study with insufficient geographic coverage. Further multicenter studies with larger sample sizes are needed to obtain more accurate and realistic data.

Numerous clinical and regional factors influence the degree of myocardial ischemia, and the FFR-CT measures the overall impact of all these individual factors. The degree of coronary stenosis cannot represent the degree of myocardial ischemia. When determining the severity of myocardial ischemia, FFR-CT is more reliable. Major clinical guidelines have gradually incorporated the functional evaluation-guided revascularization strategy. The FFR-CT is a relatively easy, quick, and affordable technique for determining the extent of myocardial ischemia. It could feasibly improve patient treatment plans, lessen the need for unnecessary invasive coronary examinations, lower medical expenses, and benefit more patients.

5 Conclusion

FFR-CT has independent predictive value for the occurrence of stable angina within a year of the examination in patients with CAD. FFR-CT technology can help clinicians make better and more reasonable assessments of cardiovascular diseases, guide them toward more informed treatment decisions for patients with CAD, and provide a more accurate prognosis.

Declarations

Ethics approval and consent to participate
The study was approved by the Clinical Application of Medical Technology and Research Ethics Committee of Hangzhou First People's Hospital, approval number: IIT-20221111-0176-01. All patients provided informed consent for participation, and the informed consent was a written document.

**Consent for publication**

All authors gave their consent for publication.

**Availability of data and materials**

All data and materials can be accessed via the corresponding author upon reasonable request.

**Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Funding**

The study was supported by the Construction Fund of Key Medical Disciplines of Hangzhou [grant number 0020200121]. The funder had a role in the collection of data and in the decision to submit the article for publication.

**Author Contributions**

YX guarantees the integrity of the study. YX and ML contributed to the conception and design. HH and ML conducted the literature search. HH, ML, YY, and YC conducted the clinical studies. HH, ML, and YY conducted the experimental analyses and data analysis. HH, ML, and YY performed the statistical analysis. HH, ML prepared the original manuscript and HH, ML, and YX edited the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

**Acknowledgments**

The authors thank Shenzhen RaySight Intelligent Medical Technology Co., Ltd. (China) for calculating FFR-CT value, and the participants and all staff members of this study for their contributions.

**References**


Figures

![Event-free survival rates for the endpoint of stable angina according to Kaplan-Meier survival analysis curves of the FFR-CT ≤ 0.80 and FFR-CT > 0.80 groups.](image)

Figure 1

Event-free survival rates for the endpoint of stable angina according to Kaplan-Meier survival analysis curves of the FFR-CT ≤ 0.80 and FFR-CT > 0.80 groups.