Advances in Cardiac Computed Tomography Functional Imaging Technology

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Keywords
Tomography · Computed tomography functional imaging · Cardiovascular disease · Cardiomyopathy · Imaging mode

Abstract
Cardiovascular disease (CVD) is the leading cause of death among patients in China, and cardiac computed tomography (CT) is one of the most commonly used examination methods for CVD. Coronary artery CT angiography can be used for the morphologic evaluation of the coronary artery. At present, cardiac CT functional imaging has become an important direction of development of CT. At present, common CT functional imaging technologies include transluminal attenuation gradient, stress dynamic CT myocardial perfusion imaging, and CT-fractional flow reserve. These three imaging modes are introduced and analyzed in this review.

Introduction
Cardiovascular disease (CVD) is the leading cause of death among patients in China [1], and cardiac computed tomography (CT) is one of the most commonly used examination methods for CVD. Since multislice helical CT has been used in clinical practice in 1998, CT hardware and software technology has made great progress. Furthermore, cardiac CT has become more and more mature, and has been widely used as the best examination method for patients with suspected coronary heart disease at present [2]. Although cardiac CT examination is excellent in the morphological evaluation of coronary arteries, evaluation of cardiac function is always the short board of CT cardiac imaging. With the continuous progress of imaging and postprocessing technology, cardiac CT functional imaging technologies are increasingly being used in clinical assessments and decision-making. Among these technologies, transluminal attenuation gradient (TAG), stress dynamic CT myocardial perfusion imaging, and CT-fractional flow reserve (FFR) have been frequently reported. In this review, the new progress of these three cardiac CT functional imaging methods was comprehensively introduced. This study aims to review and compare the differences among TAG, stress dynamic CT myocardial perfusion imaging, and CT-FFR.

Transluminal Attenuation Gradient
TAG was first proposed by Steigner et al. [3]. TAG refers to the degree of change in the CT value in the lumen of the segment of the coronary artery, beginning from the coronary artery orifice. Generally, 10 mm is used as an...
interval length to measure the CT value. The specific measurement methods are as follows. First, the cross-sectional images of the coronary artery perpendicular to the vascular centerline are reconstructed. In the segment of the coronary artery beginning from the orifice where the cross section is larger than 2 mm², the CT value in the lumen is measured at every 5 mm. Early studies have revealed that TAG generally assumes a linear trend. If there is a functional stenosis in the coronary arteries, the TAG in the lumen of the stenotic segment of the coronary artery will significantly decrease.

Choi et al. [4] revealed that compared with invasive angiography, the change in TAG is consistent with the severity of coronary artery stenosis, which helps to improve the classification of the severity of coronary artery stenosis, especially in patients with severe calcification of the coronary artery. In a subsequent study, Choi et al. [5] compared the results of TAG to FFR, with FFR < 0.8 as the boundary value, and used TAG and coronary artery CTA (CCTA) combined with the semi-quantitative method to evaluate the degree of coronary artery stenosis. It was found that the area under the receiver operating characteristic (ROC) curve significantly increased. However, the combination of these two did not significantly improve the reclassification of coronary artery stenosis. Furthermore, Yoon et al. [6] reported that compared to FFR, the area under the ROC curve of TAG was larger, but there was no statistical difference when compared to coronary arteries with a calcified plaque. Moreover, Wong et al. [7] reported that the critical value of TAG was –15.1 HU/10 mm, the sensitivity was 77%, the specificity was 74%, the positive predictive value was 67%, and the negative predictive value was 83%.

Compared with other cardiac CT functional imaging methods, TAG does not require additional scanning or complex postprocessing. Furthermore, compared with invasive FFR, TAG checks are safer, and the risk and financial burden of the examinees are lower. However, TAG also has great limitations: for patients with diffuse calcifi-
cation, due to the influence of partial volume effect and beam-hardening artifacts, there is a great difference between the measured CT value and the actual value, which will lead to the inaccuracy of the measurement results. In addition, the TAG results are also affected by coronary collateral circulation. Therefore, there is a need to maintain the stability of the CT value of the contrast agent during the scanning process. The Chinese scholars Wang et al. [8] compared TAG with corrected contrast opacification (TAG-CCO) with FFR, and revealed that CCTA-based TAG and TAG-CCO could not predict coronary artery functional stenosis. Bom et al. [9] reported that TAG, TAG-CCO, and transluminal diameter gradient did not discriminate between vessels with or without ischemia as defined by either PET or FFR. Hence, TAG or TAG-CCO combined with CCTA could not significantly improve the diagnosis of coronary artery functional stenosis.

### Stress Dynamic CT Myocardial Perfusion Imaging

In 1980, some scholars first attempted to study CT myocardial perfusion. With the development of related equipment, this technology has gradually become mature. Dual-energy CT myocardial perfusion imaging technology provides additional information about myocardial tissue composition compared with conventional single-energy CT (Fig. 1). Dual-energy CT enables evaluating the myocardial blood supply by mapping iodine distribution within the myocardium. The combined use of CCTA and CT myocardial perfusion imaging can simultaneously assess the anatomical structure and physiological functions of the coronary artery [10–20] (Table 1).

The CT myocardial perfusion imaging includes rest-stress CT perfusion (CTP) and dynamic CTP. The rest-stress CTP can obtain only one sample data, and the presence of severe CAD on CCTA may unmask balanced ischemia undetected by rest-stress CTP imaging. In stress dynamic CT myocardial perfusion imaging, the myocardial ischemia state is induced by adenosine or ATP loading. Stress dynamic CT myocardial perfusion imaging can accurately evaluate the myocardial ischemia state [21, 22]. Abnormal results of the measurement suggest that there is myocardial ischemia in the epicardium or microcirculation [23]. In at least 10–30% of patients with angina pectoris, no significant stenosis has been detected by invasive angiography, while 50–65% of these patients may have microcirculation ischemia [24–26]. A clinical trial re-

Table 1. Diagnostic efficiency of dynamic myocardial perfusion in different studies

<table>
<thead>
<tr>
<th>Research</th>
<th>Time</th>
<th>Reference criteria</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive prediction, %</th>
<th>Negative prediction, %</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bom et al. [9]</td>
<td>2019</td>
<td>SPECTICA</td>
<td>83</td>
<td>78</td>
<td>79</td>
<td>82</td>
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<tr>
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<td>86</td>
<td>98</td>
<td>94</td>
<td>96</td>
<td>NA</td>
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<tr>
<td>Wang et al. [12]</td>
<td>2012</td>
<td>SPECTICA</td>
<td>85</td>
<td>92</td>
<td>55</td>
<td>98</td>
<td>NA</td>
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<tr>
<td>Greif et al. [13]</td>
<td>2013</td>
<td>Invasive FFR</td>
<td>95</td>
<td>74</td>
<td>48</td>
<td>98</td>
<td>NA</td>
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<tr>
<td>Huber et al. [14]</td>
<td>2013</td>
<td>Invasive FFR</td>
<td>76</td>
<td>100</td>
<td>100</td>
<td>90</td>
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<tr>
<td>Rossi et al. [15]</td>
<td>2014</td>
<td>Invasive FFR</td>
<td>88</td>
<td>90</td>
<td>77</td>
<td>95</td>
<td>0.95</td>
</tr>
<tr>
<td>Bamberg et al. [16]</td>
<td>2014</td>
<td>Invasive FFR</td>
<td>93</td>
<td>87</td>
<td>75</td>
<td>97</td>
<td>NA</td>
</tr>
<tr>
<td>Bamberg et al. [16]</td>
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<td>MRI</td>
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<td>75</td>
<td>92</td>
<td>100</td>
<td>NA</td>
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<tr>
<td>Wong et al. [17]</td>
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<td>Invasive FFR</td>
<td>76</td>
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<td>NA</td>
<td>0.84</td>
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<tr>
<td>Yang et al. [18]</td>
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<td>Invasive FFR</td>
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<td>95</td>
<td>NA</td>
<td>NA</td>
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</tr>
<tr>
<td>Coenen et al. [19]</td>
<td>2017</td>
<td>Invasive FFR</td>
<td>73</td>
<td>68</td>
<td>67</td>
<td>74</td>
<td>0.78</td>
</tr>
</tbody>
</table>

AUC, area under the ROC curve; ICA, invasive coronary angiography; FFR, fractional flow reserve; NA, not available.
revealed that compared to SPECT-MPI or MRI-MPI, adenosine stress dynamic CTP has a similar accuracy in detecting myocardial perfusion defects. CTP is based on repeated imaging during the first-pass contrast agent inflow. However, De Geer et al. [27] reported that large variations in CTP blood flow suggest that a cutoff value for stress myocardial blood flow is inadequate to detect ischemic segments, and dynamic CTP was hampered by a limited coverage. Table 1 presents the published literatures on stress dynamic CT myocardial perfusion imaging in recent years. These data reveal that compared with the reference standard, CT myocardial perfusion imaging also has good sensitivity and specificity. Gao et al. [28] revealed that MBF and MBV were significantly lower in the abnormal perfusion group than in the normal perfusion group, and the differences were statistically significant. Wang et al. [29] explored the diagnostic value of the one-stop imaging of stress dynamic CT myocardial perfusion imaging combined with coronary CTA for coronary heart disease. For patients who need direct measurement of the myocardial perfusion level or patients whose images have poor quality, TAG or CT-FFR cannot yield accurate results. Hence, patients with severe calcification of the coronary artery, as well as patients with suspected coronary artery disease and negative invasive angiography results, stress dynamic CT myocardial perfusion imaging should be the first choice. At present, Lubbers et al. [30] conducted a multicenter study named CRESCENT-II, where the process of one-stop stress myocardial perfusion imaging was optimized. For patients with suspected stable chest pain, the first scanning was performed to calculate the coronary artery calcium score. For patients with a positive coronary artery calcium score, CCTA was carried out. If >50% stenosis was found in CCTA, stress myocardial perfusion imaging was performed. The study revealed that the optimized process provided a fast and efficient alternative for the function test.

### Computed Tomography-Fractional Flow Reserve

Under normal circumstances, there is no obvious resistance when blood flow is conducted through the epicardial coronary artery, that is, the intravascular pressure remains constant from near to far. However, as blood flows downstream, resistance will be increased and pressure will be de-

<table>
<thead>
<tr>
<th>Research</th>
<th>Time</th>
<th>Software</th>
<th>Types</th>
<th>Reference criteria</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive prediction, %</th>
<th>Negative prediction, %</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2011</td>
<td>HeartFlow</td>
<td>Multicenter prospective</td>
<td>Invasive FFR</td>
<td>93</td>
<td>82</td>
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<tr>
<td>Min et al. [32] (DEFACTO)</td>
<td>2012</td>
<td>HeartFlow</td>
<td>Multicenter prospective</td>
<td>Invasive FFR</td>
<td>90</td>
<td>54</td>
<td>67</td>
<td>84</td>
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<tr>
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<td>HeartFlow</td>
<td>Multicenter prospective</td>
<td>Invasive FFR</td>
<td>86</td>
<td>79</td>
<td>65</td>
<td>93</td>
<td>0.90</td>
</tr>
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<td>HeartFlow</td>
<td>Multicenter prospective</td>
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<td>57</td>
<td>83</td>
<td>62</td>
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<td>Renker et al. [35]</td>
<td>2014</td>
<td>Siemens cFFR</td>
<td>Single-center retrospective</td>
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<td>94</td>
<td>84</td>
<td>65</td>
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<td>88</td>
<td>65</td>
<td>65</td>
<td>88</td>
<td>0.83</td>
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<td>Single-center retrospective</td>
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<td>83</td>
<td>76</td>
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<td>83</td>
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<td>Meta-analysis</td>
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<td>69</td>
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<td>Invasive FFR</td>
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<td>0.78</td>
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<tr>
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<td>Siemens cFFR</td>
<td>Single-center prospective</td>
<td>Invasive FFR</td>
<td>87</td>
<td>77</td>
<td>71</td>
<td>90</td>
<td>0.89</td>
</tr>
<tr>
<td>Kishi et al. [43]</td>
<td>2018</td>
<td>Toshiba CT FFR</td>
<td>Single-center retrospective</td>
<td>Invasive FFR</td>
<td>95</td>
<td>82</td>
<td>NA</td>
<td>NA</td>
<td>0.953</td>
</tr>
<tr>
<td>Freiman et al. [44]</td>
<td>2018</td>
<td>Philips FFRct</td>
<td>Single-center retrospective</td>
<td>Invasive FFR</td>
<td>88</td>
<td>79</td>
<td>79</td>
<td>88</td>
<td>0.91</td>
</tr>
</tbody>
</table>
creased. FFR refers to the ratio of maximal blood flow in the stenotic vessel to the maximum blood flow in the normal vessel under the same condition. This was first proposed by Dr. Pijls in 1993. FFR is an index to calculate coronary blood flow through pressure measurement. It is presently recognized as a functional evaluation index to evaluate the influence of coronary artery stenosis on blood flow.

In 2014, the United States Food and Drug Administration (FDA) approved the application of a new software system (FFR-CT) of HeartFlow for the noninvasive calculation of FFR. Different from traditional cardiac catheterization, the software can detect coronary artery obstruction by noninvasive examination, and assess the coronary blood flow of coronary heart disease patients who have symptoms or signs.

Table 2 summarizes the diagnostic efficiency of CT-FFR in studies published in recent years. Among these, the DISCOVER-FLOW research published by Koo et al. [31] was the first multicenter prospective clinical trial to evaluate the diagnostic efficacy of CT-FFR. A total of 103 patients were included in that study, and the CCTA revealed at least one coronary artery with ≥50% stenosis. The diagnosis effect of CT-FFR was significantly higher than those of CCTA in terms of the accuracy of predicting coronary artery stenosis, positive predictive value, and negative predictive value. CT-FFR also has a good correlation with invasive FFR ($r = 0.678$, $p < 0.001$). Furthermore, the DeFACTO Trial [32] evaluated the diagnostic value of CT-FFR and CCTA for moderate coronary artery stenosis (30–69%). The results revealed that the negative predictive value of CT-FFR was higher than that of CCTA. Therefore, ischemic lesions requiring revascularization could be effectively screened to avoid unnecessary intervention. In the 2014 NXT research [33], a more accurate CT reconstruction technology and CT-FFR analysis software were adopted, and more strict quality control was required in the operation process of CCTA, in which all patients were required to use β-receptor blockers to control the heart rate to ≤65 bpm before CCTA, and were sublingually administered with nitroglycerin to expand the coronary artery. Moreover, the study included some patients with severe calcification, and it was found that the accuracy of CT-FFR prediction was not affected. Furthermore, due to the improvement of quality control in the process of CCTA and the analysis software, the specificity of CT-FFR was much better than that in previous multicenter studies, and had a better correlation with invasive FFR ($r = 0.82$, $p < 0.001$) [31–44] (Table 2).

A study revealed that CT-FFR could provide additional information for biomechanics in plaques, such as plaque stress, plaque strain, and radial gradient [45]. These factors play certain roles in the occurrence and pro-

![CT-FFR image. A plaque at mid CX (arrow); the CT-FFR is 0.77.](image-url)
gression of plaques [46]. This CT-FFR-derived biomechanical information is better in predicting acute coronary syndrome (ACS) than in predicting stenotic and high-risk plaques (the area under the curve is 0.727, 0.675, and 0.673, respectively; Fig. 2). In addition, CT-FFR also provides an incremental risk stratification tool. Lipid plaques with a large necrotic core and positive remodeling have been proven to be correlated to FFR < 0.8, and are independent of the degree of stenosis of the lumen. This has been proven to be an independent predictor of ACS [47, 48]. A recent study named ADVANCE [49] revealed that the abnormal rate detected by CT-FFR was significantly higher in patients with >3 risk factors than in patients with <3 risk factors. Furthermore, the multivariate analysis revealed that underlying diabetes and hypertension could predict CT-FFR abnormality.

For interpretable patients with coronary stenosis, CT-FFR should be the first choice in assessing for myocardial blood supply. FFR analysis based on CT data can evaluate the epicardial ischemia, but has limited efficacy for the evaluation of microcirculation ischemia [50]. In particular, it cannot be used to evaluate the suspected coronary heart disease patients with negative invasive angiography results. In addition, the application of CTA data for FFR analysis requires a specialized software and a long time duration. In addition, FFR analysis has a higher requirement than CTA data, which affects its routine clinical application.

Conclusion

The functional imaging of cardiac CT expands the field of cardiac CT imaging. In addition to the morphological assessment of the coronary artery, it can evaluate and test the blood supply of the myocardium. The reasonable application of these techniques can better predict myocardial ischemia, guide clinical treatment, and monitor the clinical curative effect. It has been considered that with the progress of technology, CT-FFR and CT myocardial perfusion combined with CCTA may become a powerful assessment tool for cardiovascular diseases, and will be very valuable for the accurate diagnosis of patients with suspected coronary heart disease. Cardiac CT functional imaging technology is worthy of clinical promotion and application.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of The First People’s Hospital Kashgar Region. A written informed consent was obtained from all participants.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

X.-W.T. and A.-L.M. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. R.-B.Z., L.-J.J., and Y.H. designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. X.-G.Z. coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

References

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