Coronary CTA enhanced with CTA-based FFR analysis provides higher diagnostic value than invasive coronary angiography

By Dr. M Kruk, Dr. L Wardziak, Dr. M Demkow, Dr. C Kepka

INTRODUCTION

Invasive coronary angiography (ICA) remains the gold standard for the diagnosis of coronary artery disease (CAD), and is recommended in patients with a higher probability of significant CAD, and who are potential candidates for further invasive therapies. Coronary computed tomography angiography (coroanry CTA) has recently been gaining momentum as a noninvasive and effective tool for ruling out obstructive CAD and is recommended in patients with a lower probability of CAD.

Both coronary CTA and ICA are anatomic imaging methods that have high sensitivity. On the other hand, both modalities suffer from low specificity in the detection of functionally significant coronary stenoses. Recently, it has been shown that there is no difference betweeen coronary CTA and ICA in their ability to predict which coronary stenoses could cause myocardial ischemia [1]. This diagnostic equivalence of the two modalities, coupled with the clear practical advantages of the noninvasive method (lower patient risk and costs), is already sufficient for coronary CTA to be considered as a challenger for the traditional role of ICA in CAD diagnostics.

However, in addition, recent advances involving the use of virtual fractional flow reserve (CT-FFR), i.e. FFR estimated via software using hemodynamic flow algorithms operating on coronary CTA data sets, have shown that when coronary CTA is enhanced with CT-FFR, the specificity is improved [2,3,4,5,6 &7]. This combination may actually translate into the diagnostic superiority of coronary CTA over ICA. Such a development has the potential of bringing about a profound transformation in the field of chest pain diagnostics.

In the light of this, we carried out a trial to test the hypothesis that the diagnostic accuracy of coronary CTA enhanced with CT-FFR would be higher than that of the current reference method, ICA.

The Authors

Dr. Mariusz Kruk, Dr. Łukasz Wardziak, Dr. Marcin Demkow & Dr. Cezary Kepka

Department of Coronary Disease and Structural Heart Diseases, Institute of Cardiology,

Warsaw, Poland

Corresponding author

Dr. Mariusz Kruk,

email : mariuszkruk2000@yahoo.com

STUDY DESIGN & METHODOLOGY

In a single-center prospective study we included 90 subjects with intermediate pre-test probability of CAD. The patients underwent coronary CTA and had at least one intermediate coronary stenosis (50-90%) as assessed visually on CTA; the patients were scheduled for ICA and invasive FFR.

Coronary CTA was performed using a dual source CT scanner (2x128; Somatom Definition FLASH, Siemens Medical Solutions, Forchheim, Germany) according to standard procedures. The luminal diameter stenosis was assessed using a dedicated workstation (SyngoVia, Siemens). CTA-based FFR was assessed using dedicated software (cFFR v2.1, Siemens) which is based on machine learning algorithms. Mid-diastolic reconstructed CTA datasets were analyzed on-site on the dedicated workstation to generate virtual FFR values in each location of the coronary tree based on CTA.

ICA and FFR were performed according to standard procedures, FFR was measured with the ComboWire XT guidewire (Volcano Therapeutics, Rancho Cordova, California). The pressure sensor was located beneath the most distal stenosis and the FFR was recorded during the intravenous adenosine infusion of 140 mμg/kg/min, for 3 min. A stenosis with FFR value ≤0.80 was considered to be hemodynamically significant. Coronary stenosis assessment based on ICA images was quantified using dedicated software (QCA 7.3, Medis Medical Imaging Systems BV, Leiden, Netherland) by an independent observer blinded to previous visual coronary CTA and FFR data.

The primary end-point of our trial was the comparison of the area under the ROC curves between the percentage stenoses derived either

	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Accuracy [%]
Stenosis diameter qCTA =70%	12	95	63	59	59
Stenosis diameter QCA =70%	12	98	83	60	61
Stenosis diameter qCTA =50%	78	51	54	76	63
Stenosis diameter QCA =50%	66	53	51	67	58
CTA-FFR =0,8	76	72	67	80	74

Table 1. Diagnostic parameters of qCTA, QCA, CTA based FFR for identification of significant stenosis (invasive FFR≤0.80).
PPV – positive predictive value, NPV – negative predictive value; QCA – quantitative coronary angiography, ICA – invasive coronary angiography, CTA – coronary computed tomography angiography, qCTA – quantitative coronary computed tomography

from coronary CTA or ICA alone vs the CT-FFR results, in functionally significant stenoses (invasive FFR<=0.80).

RESULTS

96 intermediate stenoses in 90 subjects (mean age 63.4 years (±8.2), 61 males) were analyzed. In 41 patients, 41 stenoses (44%) were found to be functionally significant. The median FFR value was 0.83 [IQR 0.74 to 0.90] and the median CTA-FFR value was 0.81 [IQR 0.75 to 0.89] (p=0.200). The median diameter stenoses, as assessed visually on CTA and ICA were: 70±12 and 67±11 respectively, and for quantitative assessment: 52±12 and 47±12, respectively. On CTA and ICA, respectively 95 and 93 (p=0.625) arteries had at least 50% stenosis by visual assessment, 61 and 58 (p=0.749) arteries had at least 70% stenosis by visual assessment, respectively. The detailed per-lesion diagnostic accuracy, sensitivity, specificity, PPV and NPV for visual and quantitative ICA, CTA and CTA based FFR values are shown in Table 1.

"... the use of noninvasive coronary CTA supported by CT-FFR analyses leads to more accurate diagnoses than those based on traditional, routine invasive coronary angiography...."

There was no statistically significant difference in the areas under the curve for quantitative coronary angiography (QCA), ICA, quantitative CTA (qCTA) and coronary computed tomography angiography (CTA) in the identification of significant stenosis, [Figure 2]. The AUC for CTA-based FFR for the identification of significant stenosis was 0.835 (0.745 to 0.903) and was significantly higher than any of the other AUCs [vs qCTA (p=0.010), vs QCA (p=0.004), vs CTA (p=0.007) vs ICA (p=0.004)]. Detailed data are shown in Figure 2.

SIGNIFICANCE OF THE RESULTS AND FUTURE DIRECTIONS

The results of our trial show that the triage of chest pain patients based on the use of noninvasive coronary CTA supported by CT-FFR analyses leads to more accurate diagnoses than those based on traditional, routine invasive coronary angiography. These results suggest that coronary CTA has the potential to replace ICA, which could ultimately represent a veritable revolution in coronary artery disease diagnostics.

Coronary CTA is recognized as a useful diagnostic tool in ruling out significant CAD in patients with intermediate probability of CAD

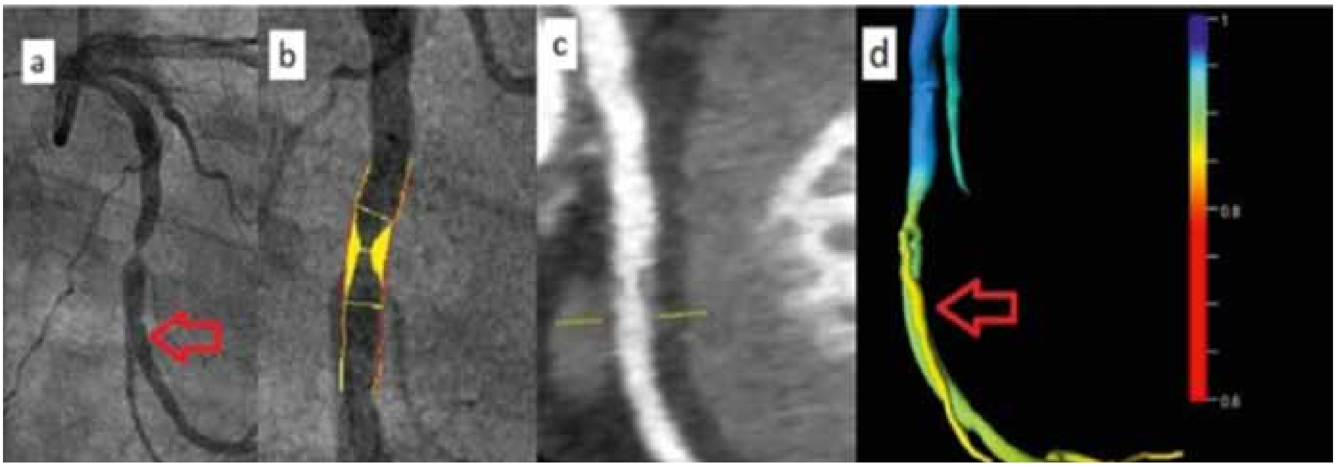
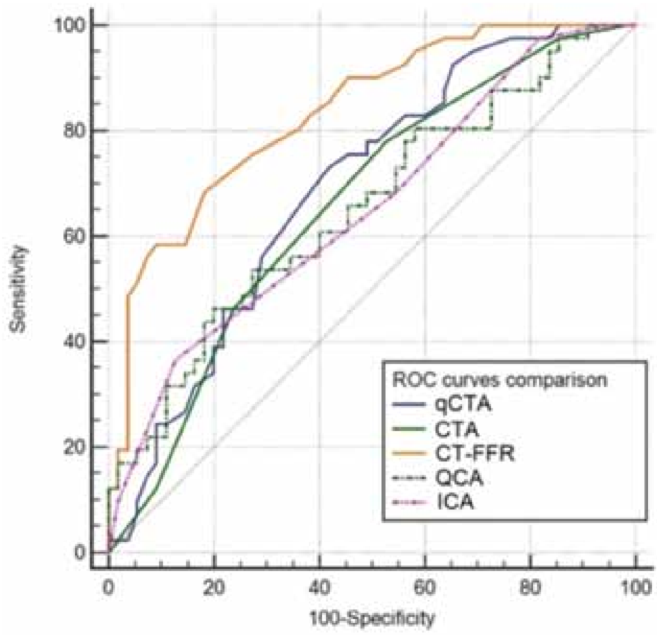


Figure 1. Examples of the imaging methods used in the trial. (a) Left circumflex (LCx) coronary artery with 80% stenosis as assessed visually on coronary CTA and ICA. The red arrow indicates the tip of the pressure wire which is located distally to the stenosis (FFR=0,92). (b) QCA measurement of the stenosis, (c) CT reconstrucion of LCx (d) color-coded CTA-FFR rendering of the LCx artery. The red arrow indicates the position where the CTA-FFR measurement was taken (CTA-FFR=0,90). The FFR and CTA-FFR results were in agreement.



	AUC	95% CI
QCA	0.653	0.549 to 0.747
ICA	0.652	0.548 to 0.746
CTA	0.660	0.557 to 0.754
qCTA	0.690	0.588 to 0.781
CT-FFR	0.835	0.745 to 0.903

Figure 2. Comparison of The Area Under Receiver Operating Characteristics Curves (ROC) for CTA, qCTA, ICA, QCA, CTA-FFR. The AUC for CTA-FFR was significantly higher than any of the other AUCs [vs qCTA (p=0.010), vs QCA (p=0.004), vs CTA (p=0.007) vs ICA (p=0.004)].

Abbreviations: QCA – quantitative coronary angiography, ICA – invasive coronary angiography, CTA – coronary computed tomography angiography, qCTA – quantitative coronary computed tomography angiography, CTA-FFR – fractional flow reserve derived from computed tomography

and, unlike any other noninvasive coronary diagnostic modality, has been shown to improve patient outcomes [7]. Several landmark studies, followed by other, smaller investigations, have focused on the evaluation of the added diagnostic value of coronary CTA-based FFR analysis compared to coronary CTA alone in predicting functionally significant coronary stenoses. The results of studies of CTA-FFR showed that the approach resulted in an improvement in specificity and positive predictive value of approximately 50% compared to coronary CTA alone, while still maintaining high sensitivity and negative predictive value [5].

Financial impact analysis of clinical studies involving CT-FFR have also shown a reduction in the overall costs of CAD diagnostics when CT-FFR is used.

Several clinically validated CT-FFR methods have been developed, based on different operational models, e.g. on-site vs off-site analysis, various algorithms (based on either *in silico* simulation or machine learning), and differing in the time needed to retrieve the results (from minutes to hours). So far, however only one method has been FDA-approved and is thus available for routine clinical purposes.

Our study reinforces the concept of the equivalence of coronary CTA with ICA in patients for whom ICA is currently indicated. This concept has been tested in two randomised trials: CAT-CAD and CONSERVE [8, 9]. The results of these trials showed that the use of CTA dramatically decreased the number of nonactionable ICAs (i.e. ICA not followed by further invasive therapies). Given the superiority of the combination of coronary CTA with added CT-FFR analysis over ICA in providing accurate diagnosis, our results may lead ultimately to the complete eradication of exploratory coronary invasive diagnostics, except for patients requiring immediate coronary intervention, such as in acute coronary syndromes.

CONCLUSIONS

Our results indicate the superior diagnostic accuracy of conventional coronary CTA diagnostics coupled with additional CT-FFR analysis over ICA in patients with intermediate coronary stenosis.

REFERENCES

1. Budoff MJ, Nakazato R, Mancini GB, *et al*. CT Angiography for the Prediction of Hemodynamic Significance in Intermediate and Severe Lesions: Head-to-Head Comparison With Quantitative Coronary Angiography Using Fractional Flow Reserve as the Reference Standard. JACC Cardiovasc Imaging. 2016;9:559-64. doi: 10.1016/j.jcmg.2015.08.021.

2. Norgaard BL, Leipsic J, Gaur S, *et al*.l & NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am CollCardiol 2014;63:1145–1155. doi: 10.1016/j.jacc.2013.11.043.

3. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;308:1237-45. doi: 10.1001/2012.jama.11274.

4. Kruk M, Wardziak Ł, Demkow M et al. Workstation-Based Calculation of CTA-Based FFR for Intermediate Stenosis. JACC CardiovascImaging. 2016;9:690-9. doi: 10.1016/j.jcmg.2015.09.019.

5. Hecht HS, Narula J, Fearon WF. Fractional Flow Reserve and Coronary Computed Tomographic Angiography: A Review and Critical Analysis. Circ Res. 2016;119:300-16. doi: 10.1161/CIRCRESAHA.116.307914.

6. Koo BK, Erglis A, Doh JH, *et al*. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am CollCardiol 2011; 58:1989–97. doi: 10.1016/j.jacc.2011.06.066.

7. SCOT-HEART investigators, Newby, DA *et al*.. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. N Engl J Med. 2018; 379(10): 924-933. doi: 10.1056/NEJMoa1805971.

8. Rudziński PN, Kruk M, Kńpka C, Schoepf UJ *et al*. The value of Coronary Artery computed Tomography as the first-line anatomical test for stable patients with indications for invasive angiography due to suspected Coronary Artery Disease: CAT-CAD randomized trial. J Cardiovasc Comput Tomogr. 2018 Nov - Dec;12(6):472-479. doi: 10.1016/j.jcct.2018.08.004.

9. Chang HJ, Lin FY, Gebow D *et al*. Selective Referral Using CCTA Versus Direct Referral for Individuals Referred to Invasive Coronary Angiography for Suspected CAD: A Randomized, Controlled, Open-Label Trial. JACC Cardiovasc Imaging. 2018 doi: 10.1016/j.jcmg.2018.09.018.