



# Noninvasive CT-based hemodynamic assessment of coronary lesions derived from fast computational analysis: a comparison against fractional flow reserve

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## Abstract

**Objectives** Application of computational fluid dynamics (CFD) to three-dimensional CTCA datasets has been shown to provide accurate assessment of the hemodynamic significance of a coronary lesion. We aim to test the feasibility of calculating a novel CTCA-based virtual functional assessment index (vFAI) of coronary stenoses > 30% and ≤ 90% by using an automated in-house-developed software and to evaluate its efficacy as compared to the invasively measured fractional flow reserve (FFR).

**Methods and results** In 63 patients with chest pain symptoms and intermediate (20–90%) pre-test likelihood of coronary artery disease undergoing CTCA and invasive coronary angiography with FFR measurement, vFAI calculations were performed after 3D reconstruction of the coronary vessels and flow simulations using the finite element method. A total of 74 vessels were analyzed. Mean CTCA processing time was 25(± 10) min. There was a strong correlation between vFAI and FFR, ( $R = 0.93$ ,  $p < 0.001$ ) and a very good agreement between the two parameters by the Bland–Altman method of analysis. The mean difference of measurements from the two methods was 0.03 (SD = 0.033), indicating a small systematic overestimation of the FFR by vFAI. Using a receiver-operating characteristic curve analysis, the optimal vFAI cutoff value for identifying an FFR threshold of ≤ 0.8 was ≤ 0.82 (95% CI 0.81 to 0.88).

**Conclusions** vFAI can be effectively derived from the application of computational fluid dynamics to three-dimensional CTCA datasets. In patients with coronary stenosis severity > 30% and ≤ 90%, vFAI performs well against FFR and may efficiently distinguish between hemodynamically significant from non-significant lesions.

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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## Key Points

- *Virtual functional assessment index (vFAI) can be effectively derived from 3D CTCA datasets.*
- *In patients with coronary stenoses severity > 30% and ≤ 90%, vFAI performs well against FFR.*
- *vFAI may efficiently distinguish between functionally significant from non-significant lesions.*

**Keywords** Coronary artery disease · Myocardial fractional flow reserve · Computed tomography angiography

## Abbreviations

CACS	Coronary artery calcium score
CAD	Coronary artery disease
CFD	Computational fluid dynamics
CTCA	Computed tomography coronary angiography
FFR	Fractional flow reserve
ICA	Invasive coronary angiography
vFAI	Virtual functional assessment index

## Introduction

Fractional flow reserve (FFR) has evolved as the invasive reference standard for functional assessment of coronary stenoses and guidelines recommend its routine application in patients undergoing ICA in the absence of previously non-invasively documented significant inducible ischemia [1]. In patients with stable CAD, FFR does not substitute the assessment of inducible myocardial ischemia, but it has proven to be superior to classical coronary anatomic parameters (i.e., stenosis severity) in guiding patients' management, reliably discriminating the coronary lesions which have hemodynamic significance and could be revascularized from those that can be safely managed conservatively, with improved patients' clinical outcome and overall resource utilization [1–3]. Nevertheless, FFR is not routinely performed in daily clinical practice, being used in less than 10% of the coronary diagnostic or interventional procedures [4], possibly due to added technical needs (i.e., need for a dedicated wire and administration of a coronary vasodilator) and higher cost [8].

In the last decade, computed tomography coronary angiography (CTCA) has become a valid diagnostic tool in different patient groups, allowing accurate non-invasive evaluation of CAD extent and severity [5, 6]. Moreover, by application of computational fluid dynamics (CFD) to coronary three-dimensional anatomical models, it has been demonstrated that CTCA allows also non-invasive assessment of the hemodynamic relevance of a coronary lesion with good diagnostic accuracy compared to invasive FFR [7–13]. A number of recent studies have suggested that quantitation of CTCA-based FFR (FFR<sub>CT</sub> - HeartFlow, Inc.) might significantly increase the diagnostic accuracy of CTCA [7, 10, 11, 14–18]. However, the current version of this technique requires a remote and lengthy core-laboratory analysis which could limit its wider clinical application. Kruk et al proposed an

alternative method using a software research prototype (cFFR version 1.4, Siemens Healthineers), which does not require a remote core-laboratory analysis [9, 19, 20], while Ko et al developed a method which still requires a core-laboratory analysis (Canon Medical Systems Corp.), but is fast with a computational time around 30 min [13].

The evaluation of virtual functional assessment index (vFAI) measured from invasive angiographic data [21] has been recently suggested as a valid alternative to FFR measurements in patients submitted to ICA, allowing to determine the hemodynamic relevance of a given coronary lesion with a few minutes long computation time. The algorithm uses three-dimensional (3D) coronary anatomical data and steady-flow CFD analysis to compute the ratio of distal to proximal pressure over the lesion for flows in the range of 0 to 4 ml/s, normalized by the ratio over this range for a normal artery, offering a measure of CAD hemodynamic significance that is numerically equal to the invasively measured FFR.

However, while vFAI measures have been successfully derived from 3D-ICA datasets, positively mimicking invasive FFR results, the possibility to compute this coronary functional parameter from CTCA-based coronary anatomical models has not yet been investigated. The first aim of the current study is to test the feasibility of assessing vFAI by using our automated in-house-developed CTCA 3D reconstruction software for generating 3D arterial models, and performing the required blood flow simulations on the aforementioned models [22]. The second aim is to evaluate the efficacy of our method by comparing the derived vFAI values to the invasively measured FFR in coronary stenoses ranging between 30 and 90%.

## Materials and methods

### Study population

This is a retrospective analysis based on the FP7 multicenter EVINCI (EVALUATION of INTEGRATED Cardiac Imaging for the Detection and Characterization of Ischaemic Heart Disease) project and part of the on-going Horizon-2020 SMARTool (Simulation Modeling of coronary ARtery disease: a tool for clinical decision support) project. The complete EVINCI protocol is available at <http://www.clinicaltrials.gov> (NCT00979199). Dedicated core-labs were responsible for harmonization of imaging protocols, quality assessment of

imaging tests, and independent imaging analysis. From the whole EVINCI population, we identified 69 patients with intermediate probability (20–90%) of CAD, who underwent both CCTA and ICA demonstrating coronary stenoses with 30–90% luminal reduction of a major vessel and in whom invasive FFR was assessed. Patients with previous acute coronary syndrome, known CAD, left ventricular ejection fraction < 35%, more than moderate valve disease, and cardiomyopathy were excluded. From the enrolled patients, those with satisfactory-to-excellent image quality of CTCA acquisition as defined by the EVINCI CTCA core-lab, based on the absence of motion artifact, image noise, or extensive coronary calcifications, were selected for evaluating the accuracy of vFAI compared to invasive FFR to predict the presence of hemodynamically significant CAD. Accordingly, from the 69 patients, 6 (8.7%) were excluded from the study due to poor image quality.

### Invasive coronary angiography and FFR measurements

ICA was performed using standard techniques and multiple projections. Quantitative analysis by ICA core-lab was available in all the selected patients. The FFR was invasively measured using a Combo-Wire (Volcano Corporation), under the administration of 140  $\mu\text{g}/\text{kg}/\text{min}$  of intravenous adenosine. Segments with FFR values  $\leq 0.8$  were considered to indicate significant stenoses.

### CTCA acquisition protocol

Coronary CTCA was performed in all of the enrolled patients, as mandated by the original protocol of the EVINCI study [23], using  $\geq 64$ -slice CT scanners. The arterial segments of interest were reconstructed in mid to end diastole (70–80% of the R–R interval) with an average slice thickness of 0.6 mm and an increment of 0.6 mm. To optimize image acquisition and final CTCA quality, beta-blockers and sub-lingual nitrates were used as per study protocol. In order to improve the interpretability of CT images and maximize the use of dose-sparing prospective ECG gating, a regular heart rate of < 65 bpm was adopted by the study protocol. Accordingly, the use of beta-blockers was encouraged in case of higher heart rates, by means of up to 25 mg of intravenous metoprolol.

The presence of coronary calcifications was evaluated in each patient by computation of calcium score (CACS), which was considered extensive if it was higher than 400 [23]. Scan quality of the CTCA was categorized by the independent EVINCI Core-Lab into four categories (i.e., excellent, good, satisfactor, and poor). Scans of poor quality were excluded from the present analysis.

### CTCA 3D reconstruction

The 3D reconstruction was performed using our in-house-developed software and the reconstruction process is carried out in seven steps, as it is described elsewhere [22].

Coronary arteries were reconstructed using the same landmarks for each patient based on the SYNTAX SCORE chart. Specifically, for RCA, the reconstructed models included segments 1–3, for the LAD artery, segments 6–8, whereas for the LCx artery, segments 11–13. The reconstruction and the vFAI calculation process are depicted in Fig. 1 (A–E).

### Virtual functional assessment index (vFAI) calculation

Blood flow simulations were performed on the 3D models of the arteries by generating a mesh of tetrahedral finite elements which then allows the solution of the appropriate Navier–Stokes and continuity equations using ANSYS® CFX 15.

For the vFAI calculation, following the method of Papafaklis et al [21], we performed two separate simulations for each case, applying flow rates of 1 and 3 ml/s, in order to create the case-specific pressure gradient ( $\Delta P$ )–flow relationship [24] for each case (Eq. 1):

$$\Delta P = 0 + f_v Q + f_s Q^2 \quad (1)$$

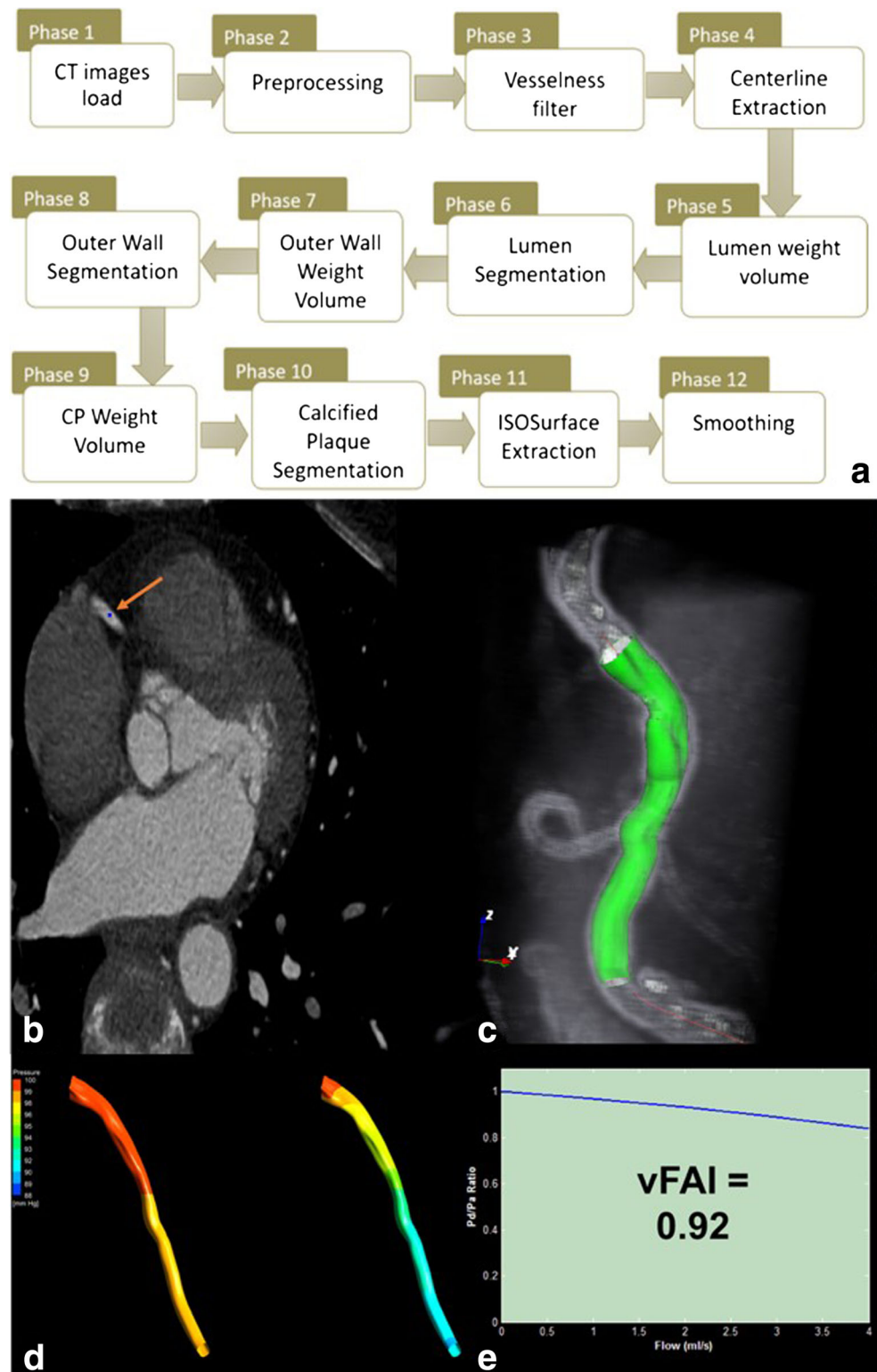
where  $\Delta P$  is the pressure gradient,  $Q$  is the flow rate,  $f_v$  is the coefficient of pressure loss due to viscous friction and  $f_s$  is the coefficient of pressure loss due to flow separation [25–27]. By solving the fully determined system of the aforementioned equation, we calculated  $P_d/P_a$  from (Eq. 2):

$$\frac{P_d}{P_a} = 1 - f_v \frac{Q}{P_a} - f_s \frac{Q^2}{P_a} \quad (2)$$

$P_a$  was set at 100 mmHg (mean aortic pressure); hence the area under the  $P_d/P_a$  vs. flow curve is then calculated for a flow range between 0 and 4 ml/s, which corresponds to the mean + 2SD increase of the hyperemic flow rate in a normal human coronary artery, initiating from an average flow rate value of 1 ml/s during rest [28]. Finally, we calculated the vFAI for each case as the ratio of the area under the artery-specific  $P_d/P_a$  vs. flow curve to the reference area, a value that has been shown to correlate well to the invasively measured FFR value [21]. Although vFAI was tested and validated on ICA-derived 3D arterial models, the fluid dynamics background of the aforementioned method may also be applicable to CTCA-derived models, since it takes into account only the geometry itself of the model of interest and not other hemodynamic or biological factors.

Image analysis was performed without prior knowledge of the FFR or ICA values by an independent reader (PS) with experience in analyzing CTCA images and using the 3D reconstruction module optimally. In vessels with multiple

**Fig. 1** **a** 3D reconstruction process flowchart. **b** Reconstruction process. The orange arrow indicates the point of the RCA that was annotated by the user. **c** 3D reconstructed artery, which is derived from the previously annotated point. **d** Pressure distribution for flow rates of 1 ml/s and 3 ml/s. The Red color indicates a pressure of 100 mmHg whereas the deep blue color indicates a pressure value of 88 mmHg. **e** Invasively measured FFR was 0.92, the same as the respective vFAI



lesions, the precise segment of vFAI measurement was selected by an independent reader (MIP) not involved in the vFAI analysis to match carefully the respective ICA segment on which invasive FFR was measured. To test interobserver agreement, the same analysis was performed in a randomly

selected subset of studies by a second reader (DL) following appropriate training. The average analysis time required for each of the assessed arteries was 25 min ( $\pm 10$  min). The required average 3D reconstruction time was around 3 min and the remaining was needed for the necessary blood flow

simulations. Two examples, one of a rather borderline case and one severely ischemic are depicted in Fig. 2.

### Statistical analysis

The relationship between FFR and vFAI was quantified by calculating the Pearson’s correlation coefficient. Bland–Altman plots and the corresponding 95% limits of agreement were used to assess the agreement between the two methods. ROC analysis was performed for identifying the cutoff values of the examined variables. Categorization of FFR and vFAI values was made using the cutoff of 0.8 and the calculated cutoff from ROC curve for the FFR and vFAI, respectively. ANOVA was used for multiple group comparisons followed by Bonferroni correction where applicable. Sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (the percentage of patients correctly diagnosed by vFAI) were used to assess the performance of vFAI. *P* values < 0.05 were considered statistically significant. Comparison ROC curves was based on the DeLong method (MedCalc software). The McNemar test was used to compare the accuracy of vFAI and CCTA to predict ischemia-causing stenosis. *P* values < 0.05 were considered statistically significant.

### Results

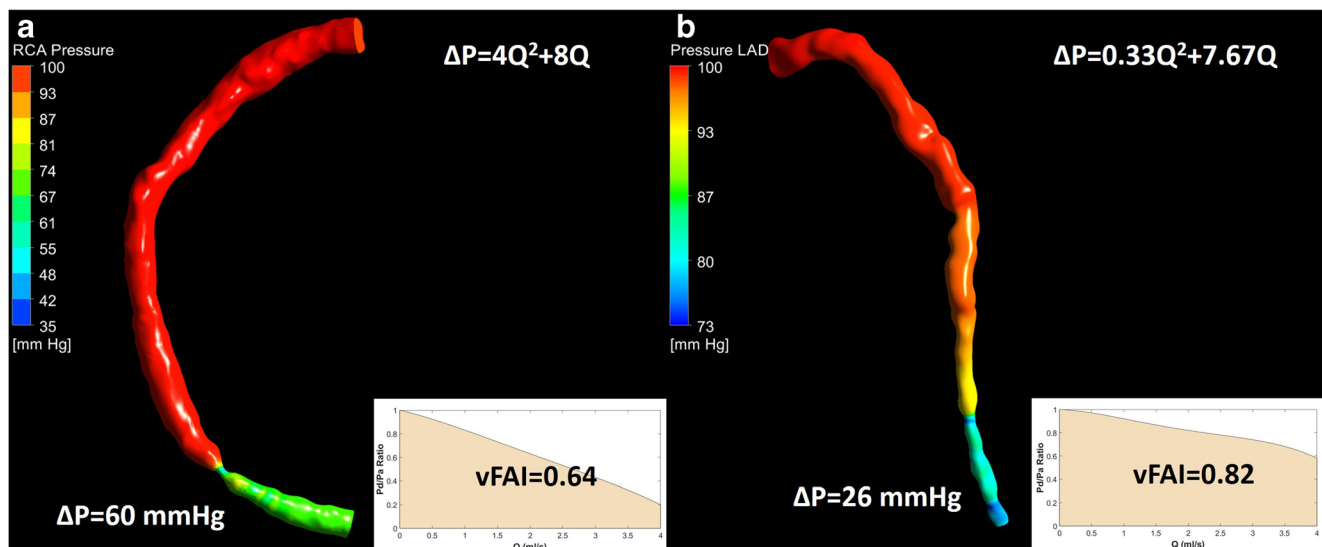
#### Baseline characteristics of the study population

The population of the present study included 63 patients (mean age 62.9 ± 7 years, 61% males) with stable symptoms.

**Table 1** Baseline characteristics of the study population (*n* = 63)

Cardiovascular risk factors	
Age	62.9 (± 7.8)
BMI, kg/m <sup>2</sup>	27.8 (± 4.9)
Body mass, kg	81 (± 15.8)
Diabetes ( <i>n</i> , %)	14 (22.2%)
Smoker during past year ( <i>n</i> , %)	16 (25.4%)
Hypertension ( <i>n</i> , %)	41 (65%)
Hypercholesterolemia ( <i>n</i> , %)	42 (66.7%)
CT coronary calcium score–Agatston ( <i>n</i> , %)	
CAC = 0	6 (9.5%)
CAC = 1–99	13 (20.6%)
CAC = 100–399	21 (33.3%)
CAC ≥ 400	19 (30.2%)
CAC not done	4 (6.3%)
Obstructive CAD ( <i>n</i> , %)	
Obstructive CAD at CTCA (> 50% stenosis)	39 (61.9%)
Obstructive CAD at ICA (> 50% stenosis)	35 (55.6%)

Hypercholesterolemia, hypertension, and CAC score > 100 were present in more than 60% of patients. The mean heart rate during the CTCA scans was 60 ± 7 beats/min. Patients’ characteristics are summarized in Table 1. A total of 74 coronary arteries with coronary stenoses ranging from 30 to 90% at quantitative ICA were interrogated by invasive FFR. The RCA was involved in 17 (25.5%), while the LAD and LCx in 42 (52.9%) and 15 (21.6%) of cases respectively. Thirty-five (47.3%), 31 (41.9%), and 8 (10.8%) coronary arteries had a 30–49%, 50–70%, and 70–90% stenoses, respectively. FFR > 0.8 was recorded in 50 vessels (67.5%), 0.75–0.80 in 9 (12.2%), and ≤ 0.75 in 15 (20.3%) vessels respectively.



**Fig. 2** Examples of ischemic cases. **a** Pressure distribution in RCA with an invasively measured FFR of 0.66 and a vFAI of 0.64. **b** Pressure distribution in LAD with an invasively measured FFR of 0.79 and a vFAI of 0.82

### CTCA-derived vFAI measurements and FFR

CTCA scan quality was defined as good–excellent for 65 (87.8%) coronary arteries and satisfactory for 9 (12.2%) vessels. The interobserver agreement for vFAI measurements was tested in 11 randomly selected coronary vessels (4 RCA, 7 LAD) (8 of good–excellent and 3 of satisfactory quality). There was a strong agreement between the two observers with no significant difference in vFAI values (mean difference = 0.0046, SD = 0.028,  $p = 0.29$ ). The intraobserver agreement for vFAI measurements was tested in 37 randomly selected coronary vessels (8 RCA, 21 LAD, 8 LCx) (31 of good–excellent and 6 of satisfactory quality). There was a strong agreement between the two measurements with insignificant difference in vFAI values (mean difference = 0.0008, SD = 0.006,  $p = 0.41$ ). FFR declined as stenosis severity increased (ANOVA  $p = 0.003$ ). Specifically, FFR was lower ( $0.74 \pm 0.1$ ) in vessels with stenoses 70–90% compared to those with stenosis severity 50–69% ( $0.83 \pm 0.08$ ,  $p = 0.033$ ) and 30–49% ( $0.86 \pm 0.08$ ,  $p = 0.02$ ). No statistically significant difference was observed in FFR values derived from vessels with stenosis severity 30–49% compared to those with 50–69% diameter stenosis ( $p = 0.55$ ). vFAI similarly declined as stenosis severity increased (ANOVA  $p = 0.015$ ). vFAI was lower ( $0.79 \pm 0.1$ ) in vessels with stenoses 70–90% compared to those with stenosis severity 50–69% ( $0.87 \pm 0.09$ ,  $p = 0.048$ ) and 30–49% ( $0.88 \pm 0.07$ ,  $p = 0.012$ ). No statistically significant difference was observed in vFAI values derived from vessels with stenosis severity 30–49% compared to those with 50–69% diameter stenosis ( $p = 1.0$ ).

There was a strong correlation between vFAI and FFR ( $R = 0.93$ ,  $p < 0.001$ ) and a very good agreement between the two parameters by the Bland–Altman method of analysis (Fig. 3). The mean difference of measurements was 0.03 (SD = 0.033,  $p < 0.0001$ ), indicating a small systematic overestimation of the FFR by vFAI. The corresponding limits of agreement were

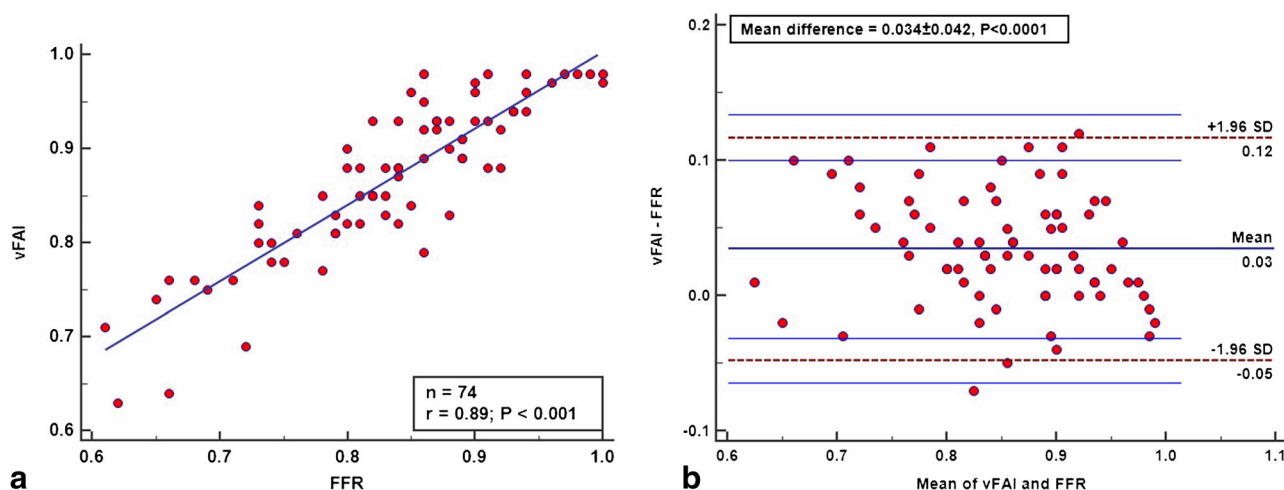
from -0.03626 to 0.09599, with 95% confidence intervals of -0.04968 to -0.02284 for the lower limit and 0.08257 to 0.1094 for the upper limit. Agreement was unaffected by calcification level. For calcified vessels with Agatston Score  $> 400$ , ( $n = 23$ ) the mean difference was  $0.036 \pm 0.065$ , whereas for milder calcifications (Agatston Score  $< 400$ ,  $n = 51$ ), the mean difference was  $0.036 \pm 0.047$ .

### Diagnostic accuracy of vFAI

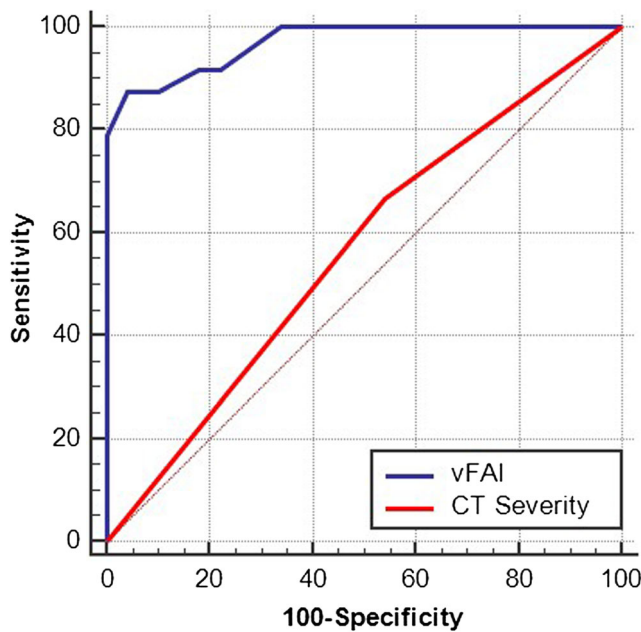
Using a receiver-operating characteristic curve (ROC) analysis, the optimal vFAI cutoff value for identifying an FFR threshold of  $\leq 0.8$  was  $\leq 0.82$  (95% CI 0.81 to 0.88). Figure 4 shows the ROC curves comparing the diagnostic accuracy of vFAI and traditional CTCA analysis (stenosis  $\geq 50\%$ ) to identify a coronary lesion with FFR  $\leq 0.8$ . Using a threshold of  $< 0.80$  as the FFR cutoff value for hemodynamically significant lesions, the overall diagnostic performance of vFAI further increases, while that of CTCA decreases. The overall diagnostic performance of vFAI and CTCA for both FFR thresholds (i.e.,  $\leq 0.80$  and  $< 0.80$ ) is presented in Table 2. The diagnostic accuracy of vFAI was significantly higher than CCTA (93.2% vs. 52.7%,  $p = 0.0027$ ).

### Discussion

We have demonstrated the feasibility of deriving an accurate index of hemodynamically significant coronary lesions through non-invasive quantitation of CTCA-based vFAI. Specifically, in a population of patients with intermediate probability of CAD and stenosis severity ranging from 30 to 90%, vFAI could be readily obtained within a short computation time, well matching the results of the accepted gold standard represented by invasive FFR. A cutoff vFAI value of  $\leq 0.82$  was associated with high sensitivity, specificity, and NPV



**Fig. 3** **a** Regression plot comparing the two methods. **b** Bland–Altman plot comparing the two methods



**Fig. 4** ROC curves comparing vFAI vs. CTCA diagnostic performance to recognize hemodynamically significant coronary lesions ( $FFR \leq 0.80$ ). The area under the curve (AUC) for the vFAI is 0.97 (95% CI 0.90–0.99,  $p < 0.0001$ ), whereas for CTCA is 0.56 (95% CI 0.44–0.68,  $p = 0.297$ )

(87.5%, 96%, and 94.1%, respectively) for identifying lesions with  $FFR \leq 0.8$ . An  $FFR$  cutoff value  $< 0.80$  resulted in even higher sensitivity and NPV [29].

A number of studies have already reported the ability of CTCA-derived functional indexes to mimic invasive  $FFR$  measurements for the detection of hemodynamically significant CAD [7, 10, 11]. In particular, while initial reports had suggested the existence of only a moderate agreement between  $FFR_{CT}$  and invasive  $FFR$  [12], recent refinements of computational techniques and CFD modelization have improved the accuracy of  $FFR_{CT}$  in unmasking the presence of hemodynamically significant coronary lesions and quantifying their severity [11]. Our results show that vFAI slightly overestimates  $FFR$  but can distinguish functionally significant from non-significant lesions with high specificity and NPV. In our study population, the cutoff vFAI value of 0.8, which has been used in prior studies, would have resulted in a low sensitivity (66.7%). Due to the slight overestimation of  $FFR$  by

vFAI demonstrated in the present study, the best cutoff value for vFAI was  $\leq 0.82$ , which increased sensitivity to levels comparable to those of similar studies without affecting significantly the specificity. Our results also demonstrate that for studies of adequate quality, coronary calcification did not affect significantly the agreement between vFAI and  $FFR$ . Intense calcification affects image quality by creating the so-called “blooming effect” leading to an overestimation of the arterial lumen and thus restricting data analysis only to studies without obvious artefactual effects. We are currently working to resolve these issues by developing a dedicated “blooming removal” algorithm and further denoising filters.

Today’s advanced computational methods are based on modeling of the physiological parameters of coronary microcirculation and vascular resistance and their influence in coronary flow during hyperemia. Considering that virtual functional assessment reflects only vessel geometry-related changes without taking into account alterations at the microcirculation level, slight disagreement between ours and other  $FFR_{CT}$  techniques regarding the optimal threshold for disease detection should be expected. The same holds true for comparisons between vFAI and ICA- $FFR$ .

Previous studies found that  $FFR_{CT}$  slightly underestimates the actual  $FFR$  values (mean difference between  $FFR$  and  $FFR_{CT}$ : Kruk et al + 0.01, Koo et al + 0.022, Min et al + 0.058, and Norgaard et al + 0.03) [7, 9–11]. These studies use a different approach regarding the calculation of  $FFR_{CT}$ , where the entire coronary vasculature is reconstructed in 3D and the lumped parameter models of the microcirculation to the out-flow boundaries are coupled but at the expense of increased computational time and need of strong computational power. Using another approach, Taylor et al [30] computed the vascular resistance and calculated the LV mass for estimating  $FFR$ . Despite the small overestimation of  $FFR$  compared to the aforementioned studies, our diagnostic accuracy is not inferior to them. In particular, diagnostic accuracy, sensitivity, specificity, PPV, and NPV for a per-vessel analysis for vFAI were 93.2%, 87.5%, 96%, 91.3%, and 94.1% whereas for  $FFR_{CT}$  were 77.1%, 56.1%, 92.7%, 85.2%, and 73.9% for the study by Kruk et al [9] (for a stenosis range of 50–90%).

**Table 2** Per-vessel DIAGNOSTIC performance for vFAI and CTCA

FFR $\leq 0.80$									
	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	TP	TN	FP	FN
vFAI $\leq 0.82$	93.2	87.5	96	91.3	94.1	21	48	2	3
CTCA stenosis $\geq 50\%$	52.7	66.7	46	37.2	74.2	16	23	27	8
FFR $< 0.80$									
	Accuracy (%)	Sensitivity (%)	Specificity (%)	sPPV (%)	NPV (%)	TP	TN	FP	FN
vFAI $\leq 0.82$	96	95.5	96.2	91.3	98	21	50	2	1
CTCA stenosis $\geq 50\%$	51.4	66.7	45.3	32.6	77.4	14	24	29	7

## Clinical implications

A preemptive non-invasive evaluation of the presence of hemodynamically significant CAD is favored by current clinical guidelines for avoiding unnecessary coronary interventions [31]. While different cardiac imaging tests can be used to rule out the presence of functionally significant CAD, a significant proportion of patients currently submitted to ICA still show no hemodynamically significant coronary lesions [32]. Many of these patients have coronary atherosclerosis that can be depicted by CTCA. A combined assessment of coronary anatomy and function is therefore desirable, but it generally requires two separate diagnostic tests resulting in higher immediate costs. Accordingly, although the advantages of a comprehensive anatomic-functional evaluation of patients with suspected ischemic heart disease have been confirmed [33, 34], such an integrated assessment is rarely performed in daily routine.

While CTCA has long represented the reference standard for the non-invasive depiction of coronary anatomy, more recently, it is also being used to obtain quantitative measures of CAD functional relevance through the modelization of coronary flow dynamics [7, 35]. The calculation of  $FFR_{CT}$ , the most validated of such functional parameters, typically requires the use of proprietary software with long computation times and a dedicated core-laboratory [10, 11]. Our results suggest that vFAI might represent a valid alternative to the more technically demanding  $FFR_{CT}$ , allowing a close estimation of invasive FFR and discriminating hemodynamically significant coronary lesions with good accuracy. The required analysis time was around 25 min that is significantly lower when compared to that of the most well-known  $FFR_{CT}$  software (1–4 h) [8] and is directly comparable to that of the study by Kruk et al (average of 20 min per case) [9], or of the study by Ko et al (average of 27 min per case) [13]. Moreover, the proposed method requires minimal user interaction regarding the 3D reconstruction process of the desired arterial segment, resulting in a good interobserver as well as intraobserver agreement.

## Study limitations

We have performed a retrospective analysis in a rather modest sample size. In particular, as the number of vessels falling within the zone with a borderline FFR value (i.e., 0.70–0.80) was 17 (23% of the total analyzed vessels), our analysis precludes definitive conclusions on the value of vFAI in such cases. On the other hand, in contrast to most previous studies, we have evaluated only patients with intermediate likelihood of CAD. In this group that is of particular clinical relevance, we have demonstrated good agreement between vFAI and FFR and our results compare well with prior studies on CTCA-based modelization of coronary flow dynamics. We acknowledge that for the time being, our method can only

perform a vessel-based reconstruction and not that of the entire arterial tree. Nevertheless, for the purposes of the current study, this was not a drawback, since we only assessed specific segments on which FFR was invasively measured. We are currently improving the algorithm to have the ability to perform a full 3D reconstruction of the entire arterial tree and this will be tested in a larger prospective study aiming to include also individuals with clinical characteristics broader than those described in the current study. Finally, striving for an almost absolute agreement between vFAI and FFR is probably an elusive task considering the intrinsic nature of vFAI. The latter mainly expresses the “potential” functional impact of anatomy, which differs fundamentally from the invasively calculated FFR that measures directly the effect of anatomy on real pathophysiologic conditions and, thus, may be influenced by the vasodilating capability of the whole coronary system.

## Conclusions

vFAI can be effectively derived from the application of CFD to three-dimensional CTCA datasets with a consistently limited computation effort. In patients with coronary stenoses 30–90%, vFAI performs well against the invasive gold standard represented by FFR and can distinguish hemodynamically significant from non-significant coronary lesions.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Constantinos D. Anagnostopoulos.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** In the context of the EVINCI study (Neglia D et al *Circ Cardiovasc Imaging*. 2015 Mar;8(3). pii: e002179. doi: <https://doi.org/10.1161/CIRCIMAGING.114.002179>), ethical approval was provided by each participating center and all subjects gave written informed consent. For the present study investigating anonymized imaging data, informed consent was waived.

**Ethical approval** Institutional Review Board approval was obtained.

## Methodology

- retrospective
- diagnostic or prognostic study
- multicenter study



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