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Research Article

Performance of the Angiography Derived FFR (vFFR) in the Evaluation of Coronary Stenoses in Comparison with FFR

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Abstract

The coronary angiography is the reference diagnostic test for the evaluation of the severity of coronary stenoses and the correspondent treatment. However, to classify an intermediate stenosis angiographically, additional evaluation must be used to confirm or negate its key features and thus the need for coronary revascularization. Therefore, Fractional Flow Reserve (FFR) was developed in order to evaluate the function of these intermediate stenoses, but still underused nowadays considering its invasive character. Computer software took place for this purpose, such as Cardiovascular Angiographic Analysis Systems (CAAS), which is based on the fluid dynamics study and the angiographic reconstruction to calculate an FFR directly derived from the angiographic image called virtual FFR (vFFR). A monocentric retrospective study done at «Grand Hôpital de l'Est Francilien», Marne-La Vallée site in France, to measure the vFFR of patients who had an invasive evaluation by means of the FFR and to compare the 2 evaluation methods of the coronary stenoses in order to determine the diagnostic performance of the vFFR.

To be able to maintain vFFR as a necessary tool in the diagnostic arsenal for non-invasive, immediate evaluation, new large scale, multicenter studies using prognostic analyses and ideally randomization protocols are needed.

Keywords: FFR, vFFR, Coronary angiography

Introduction

The coronary angiography is the reference diagnostic test for the evaluation of the coronary stenosis severity. However, the angiographic identification of an intermediate stenosis between 40 and 90% requires the use of an additional evaluation to validate or invalidate its significant character and to indicate or not a coronary revascularization [1].

The Fractional Flow Reserve (FFR) thus was developed in order to evaluate the function of these intermediate stenoses, in a situation where a non-invasive proof of myocardial ischemia was not done nor proved before.

Considering the invasive character of the FFR, this technique stays underused nowadays [2], which motivated researchers to develop new methods able to simulate it while diverting its potential risks. Thus, computer software took place for this purpose, such as Cardiovascular Angiographic Analysis Systems (CAAS) based on the fluid dynamics study and the angiographic reconstruction in order to calculate an FFR directly derived from the angiographic image called virtual FFR (vFFR). Some very recent randomized studies that took place in the last 5 years confirmed the diagnostic performance of the vFFR in comparison with FFR, which is the gold standard for the evaluation of coronary stenoses, with an excellent sensibility and specificity exceeding 90% [3,4].

The validation and generalization of this promising technique can be translated by the increase in the number of revascularized

patients showing a proof of ischemia, which serves in potentially improving the long-term prognostic of these patients.

We proposed in this work carried out within the « Grand Hôpital de l'Est Francilien » to measure retrospectively the vFFR of our patients who had an invasive evaluation by means of the FFR and to compare the 2 evaluation methods of the coronary stenoses in order to determine the diagnostic performance of the vFFR.

Methods

This is a monocentric retrospective study at « Grand Hôpital de l'Est Francilien », Marne-La-Vallée site, France. The coronary angiographies of all the patients for whom an FFR was realized between January 2022 and January 2023 were seen again and analyzed by the help of the CAAS software to calculate a vFFR. The data collection was done on April 2023.

Inclusion criteria

We have included patients older than 18 years old addressed for coronarography for: (1) a chronic coronary syndrome or equivalent ischemia (silent ischemia, left ventricular dysfunction), or (2) an acute coronary syndrome with or without ST segment elevation; In this particular case of acute coronary syndrome, the conducted study had concerned the non-culprit coronary stenoses and was realized after 48 hours of the acute phase.

Out of all the diagnostic coronarographies done in our center, we have included those with:

1. An intermediate coronary stenosis angiographically (>40% and <90%) on a main epicardial artery or one of its branches.
2. Documentation of an exact FFR value.
3. Availability of 2 angiogram acquisitions of the vessel to be studied with an angle >30 degrees between the two.

The FFR values were not known by the operators during the realization of the Vffr measurement.

Exclusion criteria

For the limits related to the reliability of the FFR from one side or for the interpretation of the angiographic image exploitation from another side, we have excluded patients having:

1. Left main stenosis
2. An aorto-ostial stenosis
3. A history of coronary artery bypass grafting on the artery to be analyzed
4. A non-analyzable coronary angiography by the software.

Results

Characteristics of the studied population

Between January 2022 and January 2023, 59 patients and 62 lesions were included for analysis.The average age of our patients was 67 years old, with extremes going from 38 to 87 years old. The sex ratio (M/F) of our patients was 3.7.

The presence of different major cardiovascular risks in our patients as well as their coronary antecedents are resumed in (Table 1).

Risk factors and antecedents	Percentage
Active smoking	22.6 %
Arterial Hypertension	64.5 %
Diabetes	37.1 %
Dyslipidemia	62.9 %
Overweight/obesity	40.3 %/24.2 %
Body mass index	27.4
Myocardial infarction	22.6 %
Coronary Angioplasty	35 %
Coronary artery bypass grafting	0 %

Table 1: Major cardiovascular risk factors and antecedents of studied patients

Among 35% of the patients having coronary angioplasty antecedents, 59% had a stent on the same artery to be analyzed and 41% were stented on different arteries, other than those comprising the lesion to be studied.

Angiographic evaluation

Coronary status

In our study, more than two third of the patients had a monovessel status (67.7%). The rest of the multivessel patients were distributed between 24.2% bivessel patients and 8.1% trivessel patients.

Only one patient had a chronic occlusion. A patient having a bivessel coronary status with a chronic occlusion of the right coronary artery associated to an intermediate stenosis of the anterior interventricular artery. This was evaluated by FFR after unblocking the contralateral artery.

Studied artery

In the majority of the cases, the studied artery was the anterior interventricular artery (62.9%). The right coronary and the circumflex represented 21% and 16.1% of the studied arteries respectively, as shown in (figure 1).

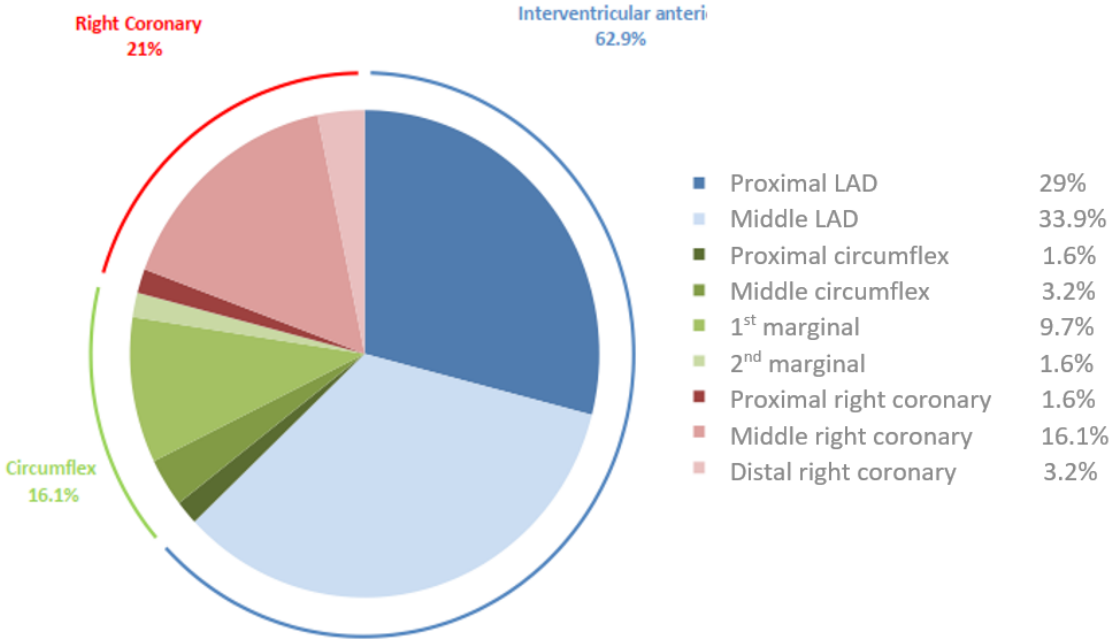

Figure 1: Distribution of lesions according to the coronary segments

Angiographic evaluation of stenoses

In our population, the average percentage of coronary stenoses, evaluated by the quantitative coronary angiography (QCA), was 54.7%, with extremes going from 40% to 80%.

The average length of the studied lesions was 22.7 mm with a minimal length and maximal length of 6 mm and 76 mm respectively.

Angiographic quantification	**Percentage of stenoses**	**54.7% ± 10**	
	Length of stenoses	**22.7 mm ± 14**	
Angiographic description	Focal stenosis	67.7 %	
	Diffuse stenosis	32.3 %	
	Moderate or important calcification	21 %	
	Tortuosities	8.1 %	
	Bifurcations	22.6 %	
	Classification MEDINA of bifurcations	0-1-0	21.4 %
		0-0-1	7.1 %
		1-1-0	50 %
		0-1-1	14.3 %
		1-1-1	7.1 %
	In-stent restenosis	6.5 %	

Table 2: Angiographic characteristics of coronary lesions.

Hemodynamic evaluation

FFR Results

The average basal FFR of our patients before hyperemia was 0.9 ± 0.05.

The average FFR after hyperemia was 0.79 ± 0.08.

A bit more than half of our patients (58.1%) had a positive FFR ≤0.8.

vFFR Results

The average vFFR of our patients was 0.8 ± 0.1.

A bit less than half of our patients (48.4%) had a positive vFFR ≤0.8.

Comparison of vFFR vs FFR

ROC curve and area under the curve

The ROC curve which represents the sensitivity in function of (1-specificity) was established.

The area under the ROC curve (AUC) thus was 0.891 (CI 95% 0.8 to 0.982) with p<0.0001.

The ROC curve for the vFFR in our study is illustrated in (Figure 2).

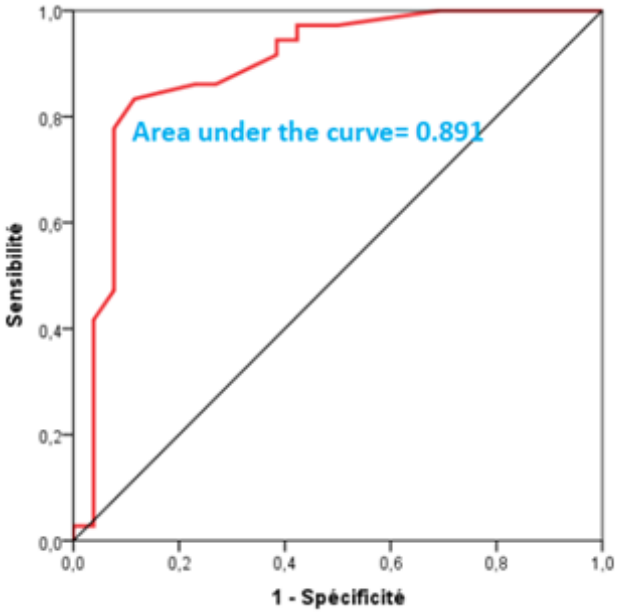

Figure 2: ROC curve for the vFFR

vFFR evaluation in the different sub-groups

Table 3 resumes the vFFR/FFR correlations in the different clinical and angiographic sub-groups in our study, using the vFFR threshold ≤0.8.

Sub-groups		Correlation vFFR/FFR	Significance (p)
Age	≥75 years old	**0.709**	**<0.0001**
	<75 years old	**0.632**	**0.015**
Sex	Men	**0.612**	**<0.0001**
	Women	**1**	**<0.0001**
Cardiovascular risk factors	Active smoking	**0.632**	**0.015**
	Arterial hypertension	**0.738**	**<0.0001**
	Diabetes	**0.840**	**<0.0001**
	Dyslipidemia	**0.706**	**<0.0001**
	Overweight/obesity	**0.739**	**<0.0001**
Antecedents	Myocardial infarction	**0.849**	**<0.0001**
	Coronary Angioplasty	0.396	0.104
Coronarography indications	CCS	**0.709**	**<0.0001**
	Thoracic pain	**0.659**	**0.001**
	Asymptomatic	**0.764**	**<0.0001**
	VG dysfunction	**1**	**<0.0001**
	NSTE-ACS	0.535	0.111
	STEMI	**1**	**<0.0001**
Coronary status	Monovessel	**0.631**	**<0.0001**
	Multivessel	**0.787**	**<0.0001**
Artery	IVA	**0.546**	**<0.0001**
	Cx	**1**	**<0.0001**
	CD	**0.639**	**0.019**
	40-60%	**0.713**	**<0.0001**
	60-70%	**0.618**	**0.003**
	70-80%	0.750	0.052
Angiographic characteristics	Focal stenosis	**0.626**	**<0.0001**
	Diffuse stenosis	**0.764**	**<0.0001**
	Calcifications	**0.617**	**0.025**
	Tortuosities	0.612	0.272
	Bifurcations	0.408	0.147
	Intra-stent restenosis	**1**	**<0.0001**

Table 3: Correlations between the vFFR and the FFR in the different sub-groups.

Discussion

Appeared in the mid-1990s, the FFR is an exploration technique that allows the study of the functional impact of a coronary lesion. If the problematic stays simple for the minimal stenoses (<40%) or very severe (>90 %), an important category of stenoses, classified as intermediate (40-90 %), has to benefit from a functional evaluation that will determine the benefit of a revascularization. The FFR allows a response to this question in the wake of coronarography, whereas, the non-invasive tests impose a strategy in two times.

We searched to clinically evaluate in our daily practice the calculation of the vFFR using the CAAS software, in comparison to the well validated reference which is the invasive measure of the FFR. Likewise, almost the majority of the studies have used the FFR as a reference diagnostic test for evaluating the diagnostic power of vFFR.

The vFFR allows to surpass complications of FFR technique given its non-invasive character apart from the specific risk of diagnostic coronarography. Another cause of insufficient use of FFR is its time-consuming nature. Indeed, Westra et al. in the FAVOR II Europe-Japan study have demonstrated a significant measurement time gain of the vFFR (5 minutes in average) in comparison with the FFR (7 minutes in average) with a $p<0.001$ [5]. All these arguments have pushed the development of software allowing the simulation of the FFR measurement based on the coronary angiography.

The reproducibility of the vFFR measurements has been well validated by Masjedi et al. in the FAST trial [3] and Pellicano et al. [6]. In fact, a low interindividual variability have been observed between operators to measure the vFFR, translating with an excellent correlation between the measured vFFR values by different operators at 0.95 ($p<0.001$) and 0.92 ($p<0.0001$) respectively in these two studies. Likewise, we have demonstrated a significant correlation between vFFR and FFR in our study at $R^2=0.692$ with $p<0.0001$. Although significant, this correlation was a bit less powerful than the one found in literature which varied between 0.69 and 0.94 [7]. In 2 recent met analysis regrouping the prospective studies comparing the vFFR with the FFR, this correlation was on average at $r=0.82$ and $r=0.8$, and these were statistically significant [8,9]. In addition, according to the FAST study that studied the vFFR calculated by the help of the same software used in our study (CAAS), the correlation was excellent at 0.89($p<0.001$) [3].

The area under the curve ROC found in our population was 0.891 (CI 95% 0.8-0.982). This testifies a very good diagnostic performance of the vFFR in the evaluation of the intermediate stenoses. These results are superimposable to big published studies as testified by the recent metanalysis of Westra and Cortés concluding to an AUC average of 0.92 (CI 95% 0.90-0.95) and 0.94 (CI 95% 0.91-0.95) respectively [8,9]. The FAST study evaluating the vFFR by means of the CAAS software concluded the same results with an AUC of 0.93 (CI 95% 0.88-0.97) [3].

The global performance in this study was improved with a threshold of 0.83 (optimal threshold found by the ROC curve). This new threshold increased the sensitivity of vFFR to above 80% (83.3%), which agrees with the majority of the published studies; this while always conserving a good specificity and diagnostic precision at 88.5% and 85.5% respectively.

Even better, the determination of both thresholds for the vFFR within the framework of a hybrid approach vFFR-FFR allowed us to suggest a new diagnostic strategy able to compensate the lack of sensitivity found in our study. The choice of these 2 thresholds vFFR ≤ 0.8 and vFFR ≥ 0.88, with recourse to the FFR if vFFR in grey zone, revealed an excellent diagnostic performance with a sensitivity and a specificity exceeding 90%. This approach has been studied and adopted by certain authors; Tar et al. have searched also to define ideal thresholds >0.88 to attain a PPV of 100% and ≤0.8 to obtain a NPV of 100%. These intervals defined in this study were found in 69% of the studied population.

In a review published in 2021, authors were searching the role of vFFR in ACS, 12 studies of angiography based vFFR trials involving patients with ACS were reviewed. A total of 2336 patients were enrolled. Accuracy of vFFR ranged from 86.8 to 95.7 and AUC ranged from 0.80 to 0.98. They concluded that vFFR should be used in intermediate lesions during an appropriate angiography to secure good results and increase the efficacy of vFFR [10].

Another review showed that although FAST trial demonstrated a good correlation between FFR and vFFR in both stable and NSTE-ACS patients ($r=0.89$ vs 0.89 respectively) with a good agreement between them (mean difference =0.01 SD =0.0356), no conclusions was made due to small sample size.

Therefore, a larger FAST EXTEND trial was conducted retrospectively on 294 patients with stable angina or NSTE-ACS to evaluate the performance of vFFR in complex lesions. Still, it confirmed a strong correlation between vFFR and FFR in different coronary vessels and lesion subsets (bifurcations, tortuous vessels, calcified lesions, tandem lesions, and diffuse disease). Furthermore, FAST II study was conducted to overcome previous limitations. However, it is a prospective trial involving six centers and 334 patients (diagnosed with stable angina or NSTE-ACS), aimed for the same purpose and showed same results. Similarly to our study, it confirmed a good correlation of vFFR with FFR but r was equal to 0.74, $p<0.001$ [11].

Limitations

Our study contains a certain number of limits

The number of patients included is relatively low (59 patients with 62 evaluated stenoses).

We did not evaluate by 2 operators the reproducibility of the vFFR measures.

Conclusion

The main interest of the vFFR is the non-invasive and instantaneous functional evaluation of the intermediate stable coronary stenoses. Besides this important contribution, some additional applications of the vFFR were described in literature, of which can even present advantages in the future compared to the FFR. Among these ones are the evaluation of the non-culprit coronary stenoses within the framework of the acute coronary syndrome with ST segment elevation by vFFR.

This work, certainly with several limits, represents a draft allowing to evaluate the interest of adopting new technologies in current practice.

Finally, an evaluation as part of a new larger study, multicentric, with a prognostic analysis, and ideally with a randomization protocol, will be necessary to be able to retain the vFFR as a needed tool in our arsenal diagnostic of non-invasive and instantaneous evaluation of intermediate stenoses and of guidance of coronary revascularizations.

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