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Angiogram based fractional flow reserve in patients with dual/triple vessel coronary artery disease☆

H. Omori [a,1], G. Witberg [b,c,*,1], Y. Kawase [a], T. Tanigaki [a], S. Okamoto [a], T. Hirata [a], Y. Sobue [a], H. Ota [a], H. Kamiya [a], M. Okubo [a], O. Valzer [b,d], R. Kornowski [b,c], H. Matsuo [a]

[a] Department of Cardiovascular Medicine, Gifu Heart Center, Gifu, Japan
[b] Department of Cardiology, Rabin Medical Center, Petah-Tikva, Israel
[c] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[d] CathWorks, Kfar-Saba, Israel

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ABSTRACT

Objective: To assess the performance of angiography derived Fractional Flow Reserve (FFRangio) in multivessel disease (MVD) patients undergoing angiography.
Background: FFR is the reference standard for physiologic assessment of coronary stenosis and guidance of revascularization, especially in patients with MVD, yet it remains grossly underutilized. The non-wire based FFRangio performs well in non-MVD patients, but its accuracy in MVD is unknown.
Methods: A prospective clinical study was conducted at Gifu Heart Centre, Japan. Patients underwent physiologic assessment of all relevant coronary lesions using wire-based FFR (wbFFR) and FFRangio. Primary outcome was diagnostic performance (sensitivity, specificity, accuracy) for FFRangio with wbFFR as reference. Other outcomes were the correlation between wbFFR/FFRangio, time required for wbFFR/FFRangio measurements, and the effect of wbFFR/FFRangio on the reclassification of coronary disease severity.
Results: Fifty patients (118 lesions in total) were included. Mean age was 72 ± 9 years, 72% were male, 36% had triple vessel disease and the average SYNTAX score was 13.
The mean measurement of wbFFR and FFRangio were 0.83 ± 0.12 and 0.81 ± 0.11, respectively. Accuracy, sensitivity and specificity for FFRangio were 92.3% (95% CI 79.1–98.4%), 92.4% (95% CI 84.3–97.2%) and 92.4% (95% CI 87.4–97.3%), respectively. Pearson's r between wbFFR and FFRangio was 0.83. FFRangio measurement was faster than wbFFR (9.6 ± 3.4 vs. 15.0 ± 8.9 min, $p < 0.001$).
Conclusions: In patients with MVD, FFRangio shows good correlation and excellent diagnostic performance compared to wbFFR, and measuring FFRangio is faster than wbFFR. These results highlight the potential clinical benefits of utilizing FFRangio among patients with MVD.

1. Introduction

Fractional flow reserve (FFR) is an index that quantifies the hemodynamic impact of a stenosis in an epicardial coronary artery [1–3]. It is defined as the ratio of hyperemic myocardial flow in the presence of stenosis, to the hyperemic flow in its absence, and is obtained by measuring the distal coronary pressure and the aortic pressure, respectively, using pressure-measuring guidewires during maximal hyperemia. FFR is considered the reference standard for clinical decision-making when intermediate stenosis is evident on the angiogram. Clinical outcome studies have shown that for non-hemodynamically significant lesions (FFR > 0.80) medical therapy should be preferred, while in cases of significant functional stenosis (FFR ≤ 0.80) coronary revascularization should be considered [4–13]. Accordingly, both the US and European revascularization guidelines recommend using FFR to guide the treatment strategy in stable coronary lesions [14,15].

Nevertheless, wire-based FFR (wbFFR) measurement incur extra costs (both for the FFR equipment and the drugs used for achieving hyperemia), produce side effects related to the need to stimulate hyperemia with vasodilators, and is time consuming. For these reasons and others, FFR utilization has remained low [16]. Therefore, the ability to derive FFR values from routinely performed coronary angiograms,

Abbreviations: CAD, coronary artery disease; FFR, fractional flow reserve; FFRCT, cardiac computed tomography derived fractional flow reserve; fSS, functional SYNTAX score; MVD, multivessel disease; PCI, percutaneous coronary intervention; SS, SYNTAX score; STEMI, ST segment elevation myocardial infarction wbFFR-wire based FFR.

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

* Corresponding author at: Department of Cardiology, Rabin Medical Center, 39 Jabotinsky Street, Petah-Tikva 49100, Israel.
E-mail address: vitberguy@gmail.com (G. Witberg).

[1] These authors contributed equally to the manuscript.

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avoiding the need for a pressure guide wire or hyperemic stimulus, could have an important impact on daily clinical practice [17,18].

Several image-based FFR methodologies have recently been introduced. Computational fluid dynamics simulation applied to cardiac computed tomography images as well as to flat detector angiograms for the evaluation of non-wbFFR have been proposed. Most of these methods require manual interaction and considerable processing time [18–24].

FFRangio™ (CathWorks, Kfar-Saba, Israel), is a novel technology providing a three-dimensional functional angiography mapping of the coronary vasculature [25]. It is based on a rapid flow analysis of a dynamically derived lumped model that can assess FFR using routine angiograms within a few minutes of automatic processing. The core algorithms estimate the functional significance of a coronary lesion, similar to wbFFR, by classifying the dynamic characteristics of the vessel as well as the subject's hemodynamic information, and provide a non-invasive measurement of FFR (see Fig. 1 for an example of the CathWorks FFRangio technology used in one of the patients included in this study).

In a prior multi-center study to validate the FFRangio technology, (sponsored by CathWorks), 203 lesions in 184 patients with wbFFR measurements underwent subsequent FFRangio analysis (offline by operators blinded to the wbFFR results). FFRangio demonstrated high correlation with wbFFR as well as high sensitivity (88%) and specificity (95%) [26]. This study included mainly single vessel disease patients with simple coronary lesions.

For patients with multivessel CAD, FFR–guided PCI has been shown to produce superior outcomes compared to angiography guided PCI for up to 5 years follow up, and is endorsed by both American and European guidelines [14]. However, wbFFR measurements in such patients are more technically challenging and time consuming. Another limitation of wbFFR is that a considerable fraction of lesions cannot be assessed due to anatomical complexity preventing pressure wire passage, as reported by investigators of the SYNTAX II and ADVISE trials [27,28]. The ability to measure FFR using noninvasive means may be especially advantageous in such patients – supplying a complete FFR estimation of the coronary tree with a single evaluation. Recently, cardiac computed tomography derived FFR (FFRCT) has shown good accuracy in detecting functionally significant lesions in patients with triple vessel disease, when compared to wbFFR [29]. Unlike FFRCT, the performance of FFRangio has not yet been evaluated in a dedicated study of patients with MVD.

The objective of this study was to estimate the efficacy of the CathWorks device in measuring FFRangio, relative to the reference standard wbFFR for diagnosing hemodynamically significant artery stenosis in patients with MVD.

2. Methods

This study was a prospective, single-center, single-arm clinical study, conducted at Gifu Heart Center (Gifu, Japan). Patients with stable angina, unstable angina or non-ST elevation myocardial infarction, with at least 1 stenosis ≥50% by visual estimation in at least 2 vessels (LAD, Circumflex and RCA) and in whom wbFFR with hyperemic stimulus was assessed at these stenoses. All patients provided written informed consent prior to enrollment in the study.

Main exclusion criteria included patients presenting with ST elevation myocardial infarction (STEMI) or presented with STEMI in the past year, chronic total occlusion in a target vessel, prior bypass surgery, surgical or percutaneous valve replacement, heart transplantation, left main disease (stenosis ≥50%), culprit lesions for NSTEMI patients (according to the judgment of the operator), in-stent restenosis and heavily diffused atherosclerosis disease.

2.1. Study procedures

2.1.1. Coronary angiography

Diagnostic coronary angiography was performed as per standard of practice using 5/6 French catheters. Operators were instructed to acquire several projections with demonstration of the entire coronary tree; the exact projections were left to the discretion of the operator.

2.1.2. wbFFR measurement

FFR measurement was performed according to the standard of care using all commercially available FFR devices (apart from the ACIST™ FFR microcatheter).

After FFR measurement, decisions regarding revascularization were made by the operator according to best clinical judgment and all available information.

2.1.3. SYNTAX score calculation

Following the angiography, the SYNTAX score (SS) for each patient was calculated using a web-based calculator [30] by an experienced operator (HO). Based on this and the wbFFR measurements, the functional SS (fSS) [31] for each patient was calculated.

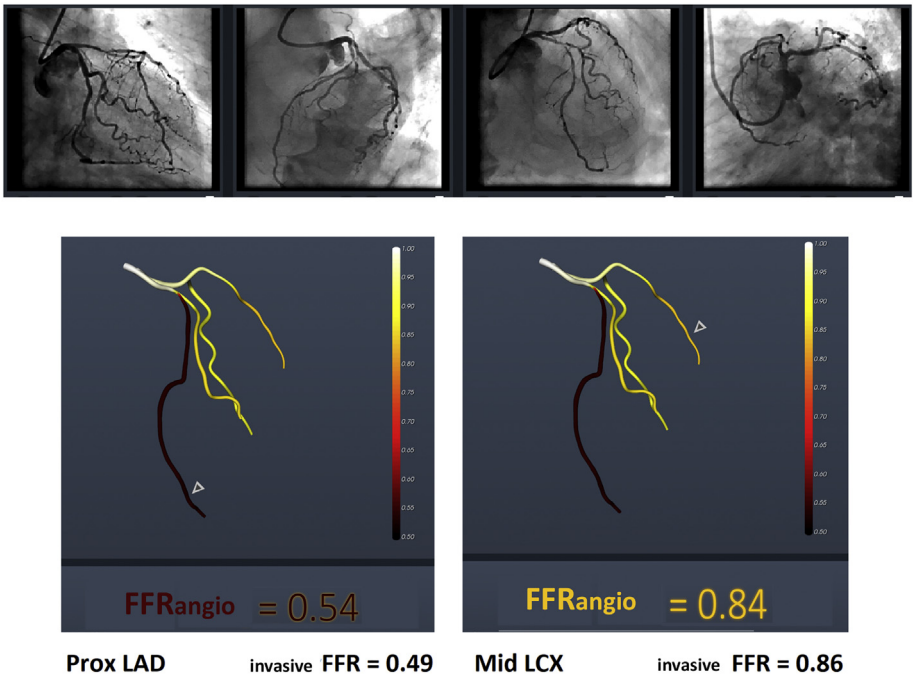

Fig. 1. An example to the use of FFRangio: 4 angiogram projections of the left coronary system in a patient with 2 vessel disease (prox LAD and mid LCx) – top panel, these projections were used to create a 3D model of the coronary system color coded according to FFRangio values at each point of the coronary arteries (middle panel), the FFRangio values for the coronary lesions are displayed (0.54 for the LAD and 0.84 for the LCx). The corresponding invasive FFR results obtained during angiography are listed below (0.49 and 0.86, respectively).

2.1.4. FFRangio measurement

Following angiography, the cine DICOM images were uploaded to a secure server and analyzed offline at the CathWorks CoreLab in Israel by an independent operator blinded to the results of the wbFFR results.

Based on the FFRangio results, the Angio based fSS for each patient was calculated.

2.2. Endpoints

The study primary endpoints included per lesion and per patient diagnostic accuracy of FFRangio in comparison to wbFFR, and sensitivity and specificity of the dichotomously scored FFRangio measured index per lesion as compared with wbFFR; Index ≤ 0.80 is scored "positive" while Index > 0.8 is negative.

Secondary endpoints included the correlation of continuously scored FFR (FFRangio and wbFFR) and the time required for measurement of FFRangio compared to wbFFR. The wbFFR timing was defined as the time elapsed from insertion of the guiding catheter to the moment the wbFFR value was available to the operator. The FFRangio timing was defined as the time elapsed from starting the CathWorks application in the designated workstation to the moment the FFRangio was available. In this study, due to regulatory constraints, the FFRangio was analyzed offline, so that DICOMs were uploaded to a secure webserver, downloaded to the CathWorks CoreLab and analyzed on a designated workstation. In a regular clinical setting (as has been performed in the recently published FAST-FFR study) [32], the CathWorks FFR software would be installed in the cathlab and analyzed online by the lab staff in the same manner.

2.3. Statistical methods

Standard summary statistics were used. The normality of measured variables was tested using the Kolmogorov-Smirnov test and inspection of Q-Q plots. Baseline characteristics of the study cohort are presented as mean ± standard deviation or median with interquartile range, as appropriate.

The correlation between FFRangio and wbFFR as continuous variable and the correlation between fSS and angio based fSS was assessed by calculating Pearson's r.

To explore the agreement between FFRangio and wbFFR, Bland–Altman analyses were plotted, and the 95% limits (1.96 * SD) of agreements were calculated.

The FFRangio result for each lesion was classified as true/false positive or true/false negative (using wbFFR as the reference standard and a value of 0.8 as the threshold for functionally significant lesions for both modalities). Categorical per lesion and per patient sensitivity, specificity, and accuracy of FFRangio were calculated.

The change in the distribution of patients according to MVD status and number of diseased vessels according to wbFFR/FFRangio was expressed with the net reclassification index (NRI) and compared by the Chi-square test.

2.4. Sample size calculation

Based on previous studies [24] we assumed a mean difference of 0.015 with a standard deviation of 0.075 between FFRangio and wbFFR. To allow for 80% power to show that the upper limit of the range of the 95% confidence interval for the Bland-Altman plot for the difference between the two measurements is below 0.20 with a significance level of 0.05, a sample size of 110 lesions was required [30]. We therefore chose a sample size of 50 patients with MVD (expecting an average of 2.5 lesions per patients), to allow for 10% attrition and meet the required sample size.

3. Results

Between August 2017 and February 2018, sixty seven consecutive patients who underwent angiography and were found to have multivessel disease requiring FFR evaluation were screened for enrollment in the study. Of these, twelve were excluded because their coronary disease fulfilled one of the exclusion criteria. Of the remaining patients, four were excluded because of violations of the angiography protocol (panning of the table and suboptimal vessel demonstration), and the DICOMs of one suitable case were lost and were not uploaded to the server. The CathWorks software could analyze the angiography images and report on FFRangio in all remaining and suitable cases. Overall fifty patients with a total of 118 lesions were enrolled in the study. The baseline characteristics are presented in Table 1. Mean age was 72 ± 9 years, 36/50 (72%) were males and 28/50 (56%) presented with stable angina. All procedures were performed using the radial access. The mean diameter stenosis by visual assessment was 64.8 ± 15.3%. The mean value of wbFFR was 0.83 ± 0.12 (range 0.46–0.99) and in 31/118 lesions (26.3%) the wbFFR value was between 0.75 and 0.85 (the "grey zone"). Intracoronary papaverine was used to stimulate maximal hyperemia in 86/118 lesions (72.9%). The mean FFRangio was 0.81 ± 0.13 (range 0.50–0.99) and in 38/118 lesions (32.2%) the FFRangio value was in the "grey zone" – see Table S1.

Table 1
Baseline characteristics.

Patient demographics	
Age	72.5 ± 9.1
Male gender, n (%)	36 (72%)
BMI	23.6 ± 3.2
Family history of CAD	5 (10%)
Hypertension	37 (74%)
Hypercholesterolemia	33 (66%)
Diabetes n(%)	13 (26%)
Smoking (current) n(%)	10 (20%)
Smoking (prior) n(%)	15 (30%)
Prior MI	1 (2%)
Prior PCI n(%)	11 (22%)
Clinical presentation	
Stable angina	28 (56%)
Unstable angina	7 (14%)
NSTEMI	15 (30%)
Procedural data	
Radial access n(%)	50 (100%)
Vessel	
RCA	24 (20.3%)
LAD/diagonal	51 (43.2%)
LCX/marginal	43 (36.4%)
Vasodilator	
IV adenosine	2 (1.7%)
IC adenosine	4 (3.4%)
IV ATP	24 (20.3%)
IC ATP	2 (1.7%)
IC papaverine	86 (72.9%)
Lesion characteristics	
Diameter stenosis (%) *visual*	64.7 ± 15.2
Diameter stenosis (%) *range*	50–90
Bifurcation	13 (10.4%)
ISR	0 (0%)
Tandem	42 (33.6%)
Collateral	0 (0%)
Calcification (*moderate-severe*)	5 (4.2%)
Tortuosity (*moderate-severe*)	45 (38.1%)
Two vessel disease	32 (64%)
Three vessel disease	18 (36%)

BMI-body mass index NSTEMI = non ST elevation myocardial infarction RCA = right coronary artery LAD = left anterior descending LCX = left circmflex IC = intracoronary ISR = in stent restenosis.

Fig. 2 presents the Bland-Altman plot for the difference between wbFFR and FFRangio. The mean difference between wbFFR and FFRangio was 0.017 ± 0.07 (95% CI −0.121 to 0.154). Pearson's r for the correlation between wbFFR and FFRangio™ as a continuous variable was 0.83 ($p < 0.001$)- see Fig. S1.

3.1. Diagnostic performance of FFRangio

On a per lesion analysis, dichotomous agreement (i.e. both measures > or ≤0.8) between wbFFR and FFRangio was achieved in 109/118 lesions (73/79 for lesions with wbFFR >0.80 and 36/39 for lesions with wbFFR ≤0.80), yielding a sensitivity of 92.3% (95% CI 79.1–98.4%), a specificity of 92.4% (95% CI 84.3–97.2%) and an overall accuracy of 92.4% (95% CI 87.4–97.3%) for FFRangio to detect functionally significant stenosis – see Table 2.

The C-statistic of the ROC curve for FFRangio was 0.92 ($p < 0.001$) - see Fig. S2.

When analyzing the 9 lesions in which there was a discrepancy between wbFFR and FFRangio, FFRangio gave a false negative result in 3 (i.e. FFRangio > 0.8 when the wbFFR ≤0.8) and in 6 lesions FFRangio gave a false positive result (i.e. FFRangio™ ≤ 0.8 when the wbFFR was >0.8).

Examples of FFRangio images and wbFFR tracings from patients with discordance between the two methods are presented in Fig. S3.

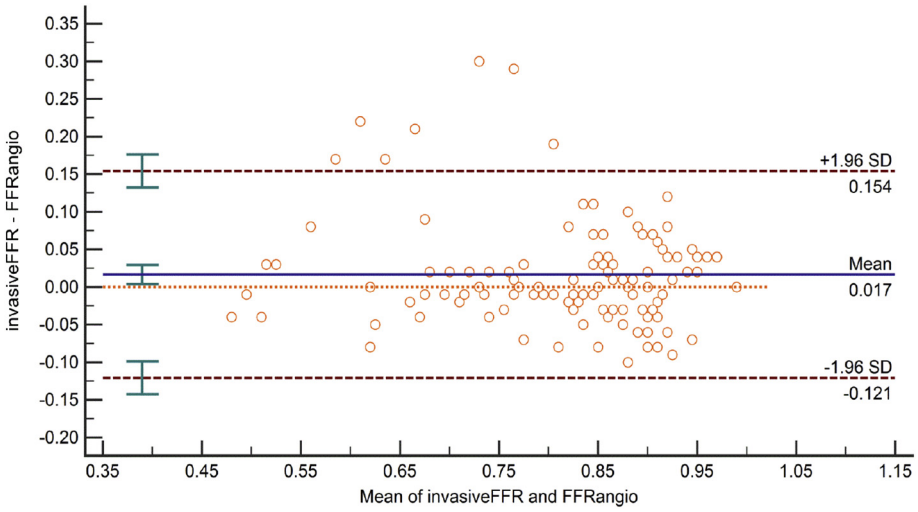

Fig. 2. Bland-Altman plot for the difference between invasive FFR and FFRangio. FFR = fractional flow reserve SD = standard deviation.

On a per patient analysis, complete agreement between wbFFR and FFRangio regarding all coronary lesions was achieved in 42/50 patients, yielding an accuracy of 84% for FFRangio - see Table 2. When comparing the characteristics of patients with concordance/discordance between wbFFR/FFRangio, all baseline characteristics were similar. The patients with discordance showed a trend for higher prevalence of RCA disease ($p = 0.09$), received iv adenosine to induce hyperemia ($p = 0.07$) and had tandem lesions ($p = 0.06$) (see Table S2) but these differences did not reach statistical significance.

The mean time required for measuring wbFFR was 15.9 ± 8.9 min per patient (6.9 ± 5.6 min per lesion), compared to 9.6 ± 3.4 (4.3 ± 3.4 min per lesion) for FFRangio, $p < 0.001$.

3.2. SYNTAX and functional SYNTAX score results

Mean SS was 13.1 ± 3.9, while the mean fSS and angio based fSS were 5.3 ± 6.8 and 5.6 ± 6.8, respectively ($p < 0.001$ for the difference between SS and fSS/angio based fSS and $p = 0.310$ for the difference between fSS and angio based fSS) – see Table S3.

Pearson's r was 0.72 for the correlation between SS and fSS, 0.67 for the correlation between SS and angio based fSS and 0.94 for the correlation between fSS and angio based fSS ($p < 0.001$ for all) – see Fig. S4.

3.3. Distribution of MVD status and number of diseased vessels

While by angiography alone, all patients were classified as having MVD (32 with two vessel disease and 18 with triple vessel disease), functional assessment had a significant effect on this classification – only 11 and 13 patients were still classified as MVD using wbFFR or FFRangio respectively (NRI = 0.78 and 0.74, respectively, $p < 0.001$ for both methods, $p = 0.625$ for the comparison between redistribution by wbFFR or FFRangio) – see Fig. S5.

Table 2
Diagnostic performance of FFRangio.

Per lesion analysis (n = 118)	
Sensitivity	92.3% (95% CI 79.1–98.4%)
Sensitivity	92.4% (95% CI 84.3–97.2%)
Diagnostic accuracy	92.4% (95% CI 87.4–97.3%)
Per patient analysis (n = 50)	
Diagnostic accuracy	84.0%

Likewise, when stratifying patients according to number of diseased vessels, functional assessment by either wbFFR or FFRangio downgraded the vast majority of patients into lower risk stratum, with no difference between the two methods (NRI = 0.84 for both, $p < 0.001$ for both methods, $p = 0.581$ for the comparison between redistribution by wbFFR or FFRangio) – see Fig. S5.

4. Discussion

This is the first study to examine the performance of angiography-derived FFR measurement in patients with MVD. Our results show that in such patients, the CathWorks FFRangio technology has excellent diagnostic performance and a high correlation with wbFFR. FFRangio has a similar effect to that of wbFFR on reclassification of coronary disease severity (as expressed by either the fSS or simpler anatomic definitions) and perhaps most importantly – is less time consuming compared to wbFFR measurement.

The ability to measure FFR across a coronary stenosis in a non-wire based method holds great potential, and over the past few years several methods for non-wbFFR assessment have been developed and are in various stages of clinical evaluation [19,20,22,24–26], most of whom have shown good diagnostic accuracy when compared to wbFFR. Of all these technologies, the largest set of data comes from using the CathWorks FFRangio system [25,26,32], which now has data on 741 lesions from 623 patients enrolled in 3 studies (including this study), consistently showing diagnostic accuracy of 92–94%.

While our results add to the growing body of evidence regarding the feasibility and accuracy of attaining non-wbFFR measurements in general, and using the CathWorks FFRangio technology in particular, it's main value lies in the fact that this is the first study to assess a non-wbFFR technology based on coronary angiogram in patients with MVD – a population that stands to gain the most benefit from this technology. For MVD patients, routine wbFFR assessment has been shown to produce better clinical outcomes for up to 2 years of follow-up [27], and equivalent results with reduced costs at 5 years when compared to angiography based PCI strategy [10]. Routine wbFFR assessment has also been shown to have a significant effect on the treatment strategy of MVD patients [33,34], with a correlation between the effect and the number of vessels assessed by wbFFR [35]. Finally, wbFFR assessment has also been shown to improve risk stratification using the SYNTAX score and its derivative residual SYNTAX score, in a way that promotes improved cost effectiveness of coronary revasculation [36]. Given all these proven benefits of

physiologic assessment in MVD patients, it is alarming that its use in routine clinical practice is very low [16].

There are a handful of reasons for the gross underuse of wbFFR in clinical practice; these include its time-consuming nature, the need to induce coronary hyperemia, and additional costs of both the FFR equipment and the drugs. Given all these limitations of wbFFR, a non-wire based approach for FFR measurement, if proven reliable, is likely to significantly increase the utilization of physiologic assessment in routine clinical practice in general, and in MVD patients in particular. Thus far, only one study reported on the performance of non-wire based FFR technology in MVD patients – a substudy of the SYNTAX II trial that evaluated FFRCT in 53 patients with triple vessel CAD [30]. The results showed fair diagnostic performance (accuracy 75% sensitivity 94% and specificity 55%). Our results show somewhat better performance for FFRangio (accuracy, sensitivity and specificity of 92%), which may be explained by the fact that our cohort was composed of MVD patients in the lower stratum of severity (mean SS of 13 and only 36% of patients with triple vessel disease compared to a mean SS II of 28 and 100% of triple vessel disease in the SYNTAX II FFRCT cohort).

If we remember the main factors hindering widespread application of physiologic assessment in the cathlab listed above, FFRangio may tackle at least three of these factors: First, it does not require the insertion of a guide wire through the coronary arteries and beyond the stenosis. Second, it does not require induction of coronary hyperemia, a quality that has been shown to be associated with increased use of invasive physiologic coronary assessment in the DEFINE REAL study, whose results showed that incorporating instantaneous wave free ratio (iFR) measurements resulted in greater use of physiologic coronary assessment compared to wbFFR only [34]. It is likely that using FFRangio will have an even greater effect on willingness to use physiologic coronary assessment, since in addition to not requiring hyperemia induction – it is also less invasive. Third, our results show that using FFRangio calculation is considerably faster than wbFFR measurement (cutting roughly a third of the time required for physiologic assessment), again, making its use more appealing and likely in daily clinical practice. It should be noted that in this study (unlike in the FAST-FFR trial [32]), FFRangio was calculated offline while wbFFR was calculated online during the procedure, but the difference in the time required for the analysis is unlikely to be explained by this, especially since this study was conducted at a center in which FFR is widely used in daily clinical practice and by operators well versed in wire-based FFR measurement, suggesting that the potential for time saving by using FFRangio may be even greater when applied to a setting in which wbFFR is less frequently used. Our results, that showed a similar effect of wbFFR and FFRangio on reclassification of coronary disease severity, either by anatomic definitions or SYNTAX score values, combined with the potential for its increased use in daily practice, illustrate the great potential FFRangio may have in the population of MVD patients.

Our study has several limitations: the sample size is moderate (although the number of lesions analyzed is larger than most studies that used non-wire based methods for FFR measurement); it is a single center study, and thus needs corroboration from more generalizable clinical settings; the FFRangio analysis was conducted offline, and although all patients enrolled qualify as MVD patients according to angiography assessment, the SS suggests that these patients were at the lower disease severity within the MVD population.

5. Conclusions

In patients with MVD, FFRangio shows good correlation and excellent diagnostic performance for detection of functionally significant coronary stenosis' when compared to wire-based FFR. Its impact on reclassification of disease severity is similar to that of wire-based FFR and it's measurement is significantly faster compared to wire-based FFR.

These results extend current knowledge on the performance of FFRangio to the MVD population, and highlight the potential benefits of its use in patients with MVD in order to optimize management strategy, long-term clinical outcomes and cost effectiveness of coronary revascularization.

Disclosure of interests

Prof. Kornowski is a co-founder and equity share-holder in CathWorks.

Dr. Valzer is an employee of CathWorks.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.072.

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