



## Comparison of diagnostic accuracy measures of novel 3D quantitative coronary angiography based software and diastolic pressure ratio for fractional flow Reserve. A single center pooled analysis of FAST EXTEND and FAST II studies

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Vessel fractional flow reserve (vFFR) has emerged as a new approach to derive fractional flow reserve (FFR) from 3D-quantitative coronary angiography (3D-QCA) without the need for an hyperemic agent or intracoronary instrumentation [1,2].

vFFR was initially validated in two retrospective, single center studies (FAST I and FAST EXTEND) [1,3]. In brief, FAST EXTEND was a retrospective single center study, in which 294 patients undergoing invasive pressure wire based FFR between January 2016 and May 2018 were enrolled [3]. FAST II conversely, was a multicenter, prospective study, which included 334 patients presenting with chronic coronary syndrome (CCS), unstable angina or non-ST-elevation acute coronary syndrome (NST-ACS), with an indication to perform pre percutaneous coronary intervention (PCI) physiological assessment [2]. In FAST EXTEND, vFFR proved to have a strong linear correlation with invasive pressure wire based FFR ( $r = 0.89$ ) and to have a high diagnostic accuracy in predicting  $FFR \leq 0.80$  lesions (AUC 0.94) [3]. Subsequently, the prospective FAST II study showed that vFFR, as calculated by either a blinded core lab or local site personnel, had an excellent diagnostic performance in predicting FFR positive lesions (AUC 0.91 and 0.93, respectively) and confirmed the optimal binary cut-off of  $\leq 0.80$ , which was initially identified in the FAST EXTEND study [2]. As such, vFFR might become an appealing alternative to conventional physiological lesion assessment using either FFR or non-hyperemic pressure ratios (NHPR) like diastolic Pressure Ratio (dPR) [2]. Using recently validated software, dPR proved to have a strong linear correlation with both iFR ( $r = 0.997$ ), and FFR ( $r = 0.77$ ) and a good diagnostic accuracy in identify lesion with  $FFR \leq 0.80$  (AUC 0.86), with a binary a cut-off of 0.89 [4,5]. However, discordance in assessment of functional lesion significance based on FFR or both vFFR and dPR has been observed in up to 20% of

cases [1,3,6]. We therefore sought to investigate the diagnostic performance of both vFFR and dPR with FFR as a reference.

In this post hoc analysis, 475 patients (mean age  $66 (\pm 9.8)$  years, 67% male) from the FAST EXTEND and FAST II studies with available pressure waveform data were included. Details on inclusion and exclusion criteria, acquisition of diagnostic angiographic projections and FFR, dPR and vFFR measurements have been previously described [1–3]. dPR was defined as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state ( $P_d/P_a$ ) over the entire period of diastole and was calculated from individual pressure waveforms using recently validated software [4]. Ethical approval was waived for both studies by the Institutional Review Board of the Erasmus University Medical Center.

Among the 475 vessels assessed, 293 (61.7%) were left anterior descending arteries, 53 (11.2%) were left circumflex arteries and 129 (27.2%) were right coronary arteries. Diffuse disease was observed in 203 (42.7%) vessels, tortuosity in 75 (15.8%) vessels, and calcific lesion in 133 (28%) vessels and 76 (16%) had bifurcation lesions.

Hemodynamically significant lesions, defined by  $FFR \leq 0.80$ , vFFR  $\leq 0.80$  and dPR  $\leq 0.89$ , were identified in 29.7%, 26%, and 31% of patients, respectively. Whereas both vFFR and dPR strongly correlated with FFR, vFFR had a significantly higher Spearman correlation with FFR than dPR ( $r = 0.82$  (CI 0.77–0.87) versus  $r = 0.72$  (CI 0.66–0.79),  $P < 0.001$  Fisher's  $r$  to  $z$  transformation) (Fig. 1). Sensitivity, specificity, and diagnostic accuracy of vFFR  $\leq 0.80$  versus dPR  $\leq 0.89$  for FFR  $\leq 0.80$  were 76% vs 79% ( $P = 0.42$ ), 94% versus 89% ( $P = 0.004$ ), and 0.89 versus 0.86 ( $P = 0.14$ ), respectively (Fig. 1). The AUCs of vFFR  $\leq 0.80$  and of dPR  $\leq 0.89$  for FFR  $\leq 0.80$  were 0.94 (95% CI, 0.925 – 0.964) and 0.89 (95% CI, 0.859 – 0.920) respectively. Differences in

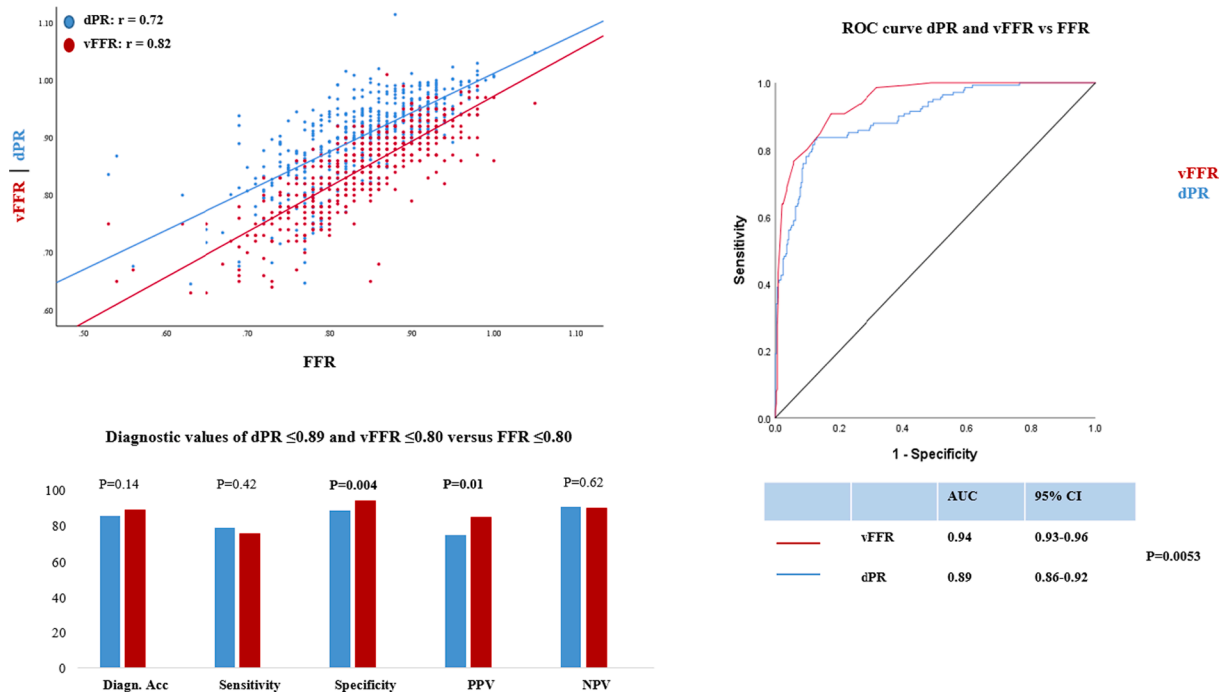
**Abbreviations:** AUC, area under the curve; CCS, chronic coronary syndrome; CI, confidence interval; dPR, diastolic Pressure Ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NHPR, non-hyperemic pressure ratios; NST-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention;  $P_d/P_a$ , distal coronary pressure/ aortic pressure; QFR, quantitative flow ratio; vFFR, vessel fractional flow reserve.

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**Fig. 1.** Comparison of diagnostic accuracy of vFFR vs dPR for FFR. (A) Correlation between vFFR and FFR (red) vs dPR and FFR (blue). (B) Diagnostic performance of dPR  $\leq 0.89$  (blue) and vFFR  $\leq 0.80$  (red) versus FFR  $\leq 0.80$  and (C) ROC curve of vFFR (red) and dPR (blue) to predict FFR positive lesions. dPR = diastolic Pressure Ratio; FFR = fractional flow reserve; vFFR = vessel fractional flow reserve; 95% CI = Confidence Interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

AUC between the indices were statistically significant and vFFR appeared to be a better discriminator of FFR than dPR ( $P = 0.0053$ ) (Fig. 1).

Discordance between vFFR and dPR was observed in 78/475 (16%) cases: among these cases, we found that vFFR was more often concordant with FFR than dPR (58% vs 42%,  $p = 0.001$ ).

Recently, an exploratory study, compared quantitative flow ratio (QFR) and instantaneous wave-free ratio (iFR) with FFR as reference and demonstrated that QFR had a stronger correlation and better diagnostic agreement with FFR than iFR [7].

Considering that vFFR is computed using a mathematical algorithm estimating the hyperemic status of the coronary circulation, the better correlation and diagnostic agreement of vFFR than dPR with FFR appears plausible. However, differences in modelled hyperemic flow (vFFR) vs. actual observed hyperemic flow (FFR) might explain a certain percentage of discordance in particular patient subsets that have an attenuated or dampened response to the induction of hyperemia.

Nevertheless, the present findings support the use of vFFR as a less invasive method with a good diagnostic performance compared with both dPR and FFR in the hemodynamic assessment of coronary lesion severity, with the potential to extend the uptake of physiology guided PCI and thus improving patient outcome.

In conclusion, in this pooled analysis of the two largest vFFR studies to date, we observed that: (a) the correlation between vFFR and FFR was significantly higher than that between dPR and FFR, (b) vFFR appears to be a better discriminator than dPR in predicting physiologically significant lesion as determined by FFR  $\leq 0.80$ , (c) in vFFR-dPR discordant cases, vFFR was more often concordant with FFR than dPR.

Limitations of our analysis include lack of clinical follow up and off-line computation of dPR. Moreover, non-availability of pressure waveform data for patients treated outside the Erasmus MC precluded dPR computation in all FAST II patient.

Currently ongoing large randomized outcome trials should further explore the clinical value of vFFR in coronary physiology guided PCI.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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