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Correlation of Fractional Flow Reserve with Ischemic Burden Measured by Cardiovascular Magnetic Resonance Perfusion Imaging

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Short Title: Correlation of FFR with CMR

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Abstract

Cardiovascular Magnetic Resonance (CMR) perfusion imaging and Fractional Flow Reserve (FFR) assess myocardial ischemia. FFR measures the pressure loss across a stenosis determining hemodynamic significance but does not assess the area subtended by the stenotic vessel. CMR perfusion imaging measures the extent of myocardial blood flow reduction (= ischemic burden). Both techniques allow for continuous rather than categorical evaluation but their relationship is poorly understood. This study investigates the relationship between the FFR value and the extent of myocardial ischemia. 49 patients with angina underwent CMR perfusion imaging. FFR was measured in vessels with a visual diameter stenosis >40%. The extent of ischemia for each coronary artery was measured by delineating the perfusion defect on the CMR images and expressing as a percentage of the LV myocardium. The correlation between the extent of ischemia measured by CMR and FFR was good ($r = -0.85$, $p < 0.0005$). The mean FFR value was 0.67 ± 0.17 and the mean perfusion defect was $8.9 \pm 9.3\%$. An FFR value of ≥ 0.75 was not associated with ischemia on CMR. The maximum amount of ischemia ($23.0 \pm 1.5\%$) was found at FFR values between 0.4 - 0.5. In patients with one vessel disease (49%) the mean ischemic burden was $15.3 \pm 8.3\%$. In patients with 2 vessel disease (18%) the mean ischemic burden was $26.0 \pm 12\%$. Reproducibility for measurement of ischemic burden was very good with a Kappa coefficient ($k = 0.826$, $p = 0.048$). In conclusion, there is good correlation between the FFR value and the amount of myocardial ischemia in the subtended myocardium.

Key words:

Ischemia

CMR perfusion imaging

FFR

Coronary artery disease

Background

In patients with stable coronary artery disease, international guidelines recommend proof of ischemia before revascularization¹. This is based on an accumulating body of evidence showing improved outcome by guiding decisions on revascularization based on the

presence of ischemia²⁻⁵. This can be done non-invasively with myocardial perfusion imaging or invasively in the catheterization laboratory with the measurement of Fractional Flow Reserve (FFR). FFR is calculated as the ratio between aortic and distal coronary flow and allows differentiation between flow limiting and non-flow limiting lesions. FFR was initially validated against SPECT and DSE⁶⁻⁸ and later against outcome^{4,5}. FFR does not, however, measure the amount of myocardium subtended by the stenotic vessel. CMR perfusion imaging allows non-invasive assessment of ischemia by visualizing the first pass of a contrast agent bolus through the myocardium. It enables direct visualization of a perfusion defect and therefore allows calculation of ischemic burden as a percentage of the myocardium. CMR first pass perfusion imaging is well validated against microspheres^{9,10}, outcome¹¹ as well as in large prospective studies^{12,13}. In clinical practice a FFR cut-off value of 0.8 is used for guiding patient management. For perfusion studies, a cutoff value of 10-12.5% ischemic myocardium for SPECT and 2-3 (out of 32) myocardial segments for CMR has been recommended to define moderate to severe ischemia¹⁴. Several studies have compared the diagnostic accuracy of CMR perfusion imaging and FFR¹⁵⁻¹⁷. However, a direct comparison between the FFR value and the ischemic burden measured by CMR has not previously been done. In this study, we sought to determine the relationship between FFR and ischemic burden measured by high resolution CMR imaging.

Methods

A total of 49 patients with typical symptoms (CCS class 1, 2 or 3) of angina were recruited into the study. They underwent CMR perfusion imaging and then angiography with FFR measurement within one month. The local research ethics committee approved the study and all patients gave written informed consent to participate. Exclusion criteria were any contra-indications to CMR scanning (i.e. claustrophobia, metallic implant, pacemaker insertion), contra-indications to adenosine therapy, previous coronary artery bypass grafts (CABG), recent myocardial infarction (MI) (within 6 months) and left ventricular (LV) ejection fraction <30%.

Data were acquired with a 1.5T scanner (Achieva, Philips, Best, The Netherlands) using 32-channel coils. Examinations included high-resolution perfusion, cine and scar imaging. Perfusion imaging consisted of 3 short axis slices acquired every heartbeat covering 16 of the standard myocardial segments (apex excluded)¹⁸ first during adenosine stress (140µg/kg/minute of adenosine administered intravenously for 4 minutes) followed by a short axis cine imaging stack and then rest imaging. Imaging parameters for perfusion

imaging: k-t blast acceleration factor 5, SSFP sequence, shortest TE (range 1.35-1.54ms), shortest TR (range 2.64-3.12ms), 50° flip angle; 90° prepulse, 100ms prepulse delay and typical acquired resolution 1.7 x 1.9 x 10mm. A dual bolus¹⁹ (equal volumes of 0.0075mmol/kg followed by 0.075mmol/kg after a 20 second pause) of weight adjusted contrast agent (Gadobutrol/Gadovist, Bayer Healthcare, Germany) was injected at 4ml/s by a power injector for stress and rest imaging. The cine images were completed with a set of long axis views. Late gadolinium enhancement (LGE) images were acquired after 10 minutes (Gadovist 0.2mmol/kg cumulative dose) using an inversion recovery sequence.

Two independent observers blinded to the angiographic data and clinical history analyzed the CMR perfusion images. A perfusion defect was defined as reduced contrast uptake at stress persisting for ≥ 4 consecutive dynamic time points but not present at rest. Each observer independently delineated LV endocardial and epicardial borders in all three slices to determine total myocardial area (Osirix software version 5.5.1. Pixeo, Switzerland). The ischemic area was delineated manually with the area of hypo-perfusion defined as the area with the least signal intensity (hypo-enhancement) in the stress perfusion dynamic with the clearest delineation of a perfusion defect. In patients with single vessel disease and one perfusion defect, the ischemic percentage was defined for that vessel as the area of hypo-enhancement normalized to ventricular area as calculated above. In multi-vessel disease, with two distinct perfusion defects it was possible to apply the same principle. In a confluent area, if it was difficult to distinguish two separate territories, then an arbitrary 50% division was applied to each. Global ischemic burden was calculated by summing the individual perfusion defects. Designation of vascular territories was done according to American Heart Association (AHA) 16-segment classification²⁰. In the presence of scar identified as areas of hyper-enhancement on late gadolinium imaging, the area of scar was quantified manually and subtracted from the area of hypo-enhancement. Inter-observer variability was determined by the comparison of the results from the two observers. Repeating the analysis of 10 cases after an interval of two weeks assessed intra-observer variability.

Standard angiographic views using a Judkin's technique were obtained. The procedure was covered with a weight-adjusted dose of unfractionated heparin. Pressure measurements were obtained in all coronary arteries with a diameter >2 mm and $>40\%$ stenosis by visual assessment using a 0.014-inch intracoronary pressure wire (Volcano Therapeutics, San Diego, CA, USA, or Pressure-Wire Certus, St Jude Medical Systems AB, Uppsala, Sweden), during hyperemia (intravenous adenosine infused at 140 μ g/kg/min for

three minutes). FFR was calculated as P_d/P_a , where P_d and P_a are distal coronary and aortic pressure respectively. A FFR of <0.75 was considered significant. Coronary occlusions or lesions of $\geq 99\%$ were categorized as FFR-positive and a default FFR value of 0.5 was assigned. In cases of serial stenoses, the pressure sensor was positioned beyond the most distal lesion and if the FFR was positive, this was ascribed to the most proximal lesion

Angiographic data was analyzed offline at the end of the study. Coronary dominance was designated on the basis of the origin of the posterior descending artery. Quantitative assessment of coronary artery percent narrowing was performed with MDQM-QCA (Medcon Limited, Tel Aviv, Israel) software. Entirely smooth and occluded arteries were allocated 0% and 100% respectively.

Data analysis was performed with SPSS version 20 (SPSS Inc., Chicago Illinois). Continuous variables were presented as mean $\pm$ SD. Correlations between normally and non-normally distributed variables were tested by Pearson's and Spearman's methods respectively. Separate analyses were done, including and excluding the CTO data which had been assigned a default value of 0.5. Normality of distribution was tested by the Shapiro-Wilk test. Differences in means between groups were compared using the ANOVA test for normally distributed populations and the Kruskal-Wallis test for non-normally distributed populations. Inter-observer variability of perfusion analysis was calculated using the kappa coefficient. Intra-observer variability was assessed by the use of the coefficient of variation from duplicate measurements.

Results

The study protocol was successfully completed in all patients. Four scans had to be excluded from the CMR analysis due to uninterpretable CMR images, either due to the presence of artefact or the basal slice being too high to allow for accurate assessment of ischemic burden. The further analysis relates to the remaining patients. The demographic and clinical characteristics of these patients are listed in table 1.

Of all 147 arteries, 59 arteries had a stenosis $>40\%$ and were assessed with FFR. 8 vessels were occluded. FFR done within the diagonal ($n=4$) and marginal branches ($n=2$) was included in the analysis of left anterior descending (LAD) artery and circumflex (CX) artery territories. No distal right coronary artery (RCA) branches were assessed. For angiographic details see table 2 and details of the CMR stress perfusion imaging hemodynamic response are given in table 3.

There was very good correlation between the FFR values and the extent of ischemia

in all territories. Analysis 1 (including occluded vessels): the mean FFR value was 0.67 ± 0.17 and the mean CMR perfusion defect size was $8.92 \pm 9.3\%$. The correlation coefficient was $r = -0.85$, $p < 0.0005$. See fig 1. Analysis 2 (excluding occluded vessels): the mean value FFR value was 0.69 ± 0.17 and the mean CMR perfusion defect size was $8.39 \pm 9.4\%$. The correlation coefficient was $r = -0.85$, $p < 0.005$.

When considering the different arterial territories individually, the correlation remained good within the LAD and RCA group: LAD $r = -0.85$ ($p < 0.005$) RCA $r = -0.81$ ($p < 0.005$), the numbers were too small to calculate significance within the circumflex group. See Figure 3. There was no significant difference between the mean values of the three groups: LAD FFR 0.71 ± 0.15 , CMR perfusion defect size $7.66 \pm 9.0\%$; CX FFR 0.70 ± 0.21 , CMR perfusion defect size $9.6 \pm 10.7\%$; RCA FFR 0.61 ± 0.19 , CMR perfusion defect size $12.2 \pm 10.2\%$; $H = 2.178$, $p = 0.336$. See table 4.

When considering lesion location within the coronary arteries (analysis done for LAD only), mean values are as follows, Proximal LAD: FFR 0.65 ± 0.11 , CMR perfusion defect $10.3 \pm 8.78\%$; Mid LAD FFR 0.68 ± 0.20 , CMR perfusion defect $8.1 \pm 10.4\%$.

At FFR values greater than 0.75, there was no myocardial perfusion defect in any patient. At values between 0.4–0.8 a linear relationship between FFR and CMR with very good correlation was found ($r = -0.83$, $p < 0.005$) See Figure 3. The FFR values that correspond to an ischemic burden of between 10 – 12.5% are 0.64 and 0.67 respectively and are also demonstrated on figure 3.

The amount of ischemia demonstrated by the extent of perfusion defect by CMR reached a peak between FFR values of 0.5– 0.4 (mean perfusion defect size: $23.0 \pm 1.5\%$). For FFR values < 0.4 less ischemia was found by CMR (mean value $15.6 \pm 3.2\%$). There was a statistically significant difference between these three groups: $H = 35.141$, $p < 0.005$. See table 4.

There was good correlation between the two observers in the measurement of CMR ischemia with a Kappa coefficient ($k = 0.826$, $p = 0.048$). Assessment of intra-observer variability demonstrated a coefficient of variation of 13% with a standard deviation of 0.3319.

Discussion

This study demonstrates a number of findings:

- 1) FFR values between 0.75 and 0.4 correlate closely with the ischemic burden as determined by CMR perfusion imaging.
- 2) An FFR value of greater than 0.75 is associated with no myocardial ischemia.
- 3) The most extensive myocardial ischemia is demonstrated for FFR values between 0.4 and 0.5.
- 4) The maximum amount of ischemia caused by one artery is 25% of the myocardium.
- 5) A 10-12.5% ischemic burden by CMR is found at FFR values of 0.64-0.67

FFR is an index of the physiological importance of a particular stenosis and its effect on flow within the artery and therefore indicates the presence of a flow-limiting stenosis²¹. Currently, a significant FFR is used as a dichotomous variable signifying presence or absence of myocardial ischemia. However, the relationship between FFR value and extent of myocardial ischemia is poorly understood.

We have shown that there is good correlation between the severity of a narrowing and the amount of ischemia present at a myocardial level. This is important for a number of reasons: firstly, it further validates the utility of FFR for the functional assessment of coronary lesions. Secondly, it demonstrates for the first time that the severity of FFR is related to the extent of myocardial ischemia. A larger pressure drop across a coronary stenosis is indicative of a greater flow limitation resulting in a lower FFR value. Our study confirms that this relationship also translates into a larger ischemic burden. Thirdly, it allows the development of FFR as a tool to assess ischemic burden.

Our results demonstrate that the maximum amount of myocardium subtended by all three arteries is consistent (20 – 25%). While the study was not designed to subdivide FFR lesions to their exact anatomical location we found greater ischemia in proximal LAD lesions in comparison to mid LAD lesions despite similar FFR values.

A study by Leone et al investigated the relationship between FFR and the amount of myocardium perfused further and demonstrated that an angiographically intermediate lesion is more likely to be functionally significant if there is a larger amount of perfused myocardium subtended by the stenosis²². They analyzed 213 intermediate stenoses (30-80% visual estimate) in 184 patients and found that lesions located in the proximal LAD were related to significantly lower FFR values and to a higher rate of positive FFR than those in the distal LAD, CX and RCA. However, this study is limited by lack of direct visualization of the amount of ischemia caused which is calculated indirectly by myocardial jeopardy scores instead.

In addition to lesion location, the relationship between FFR, diameter stenosis and minimal lumen area has also been previously demonstrated²³. However, it is noteworthy that in our study, even without controlling for similar lesion location and arterial diameter, we have demonstrated good correlation, suggesting that the actual FFR value may be one of the more important variables affecting extent of ischemia.

This phenomenon has been investigated in a recently published meta-analysis, which also explores FFR as a continuous variable. Data from approximately 7000 patients was collated including the follow up for clinical events. The authors undertook a lesion level analysis which demonstrated that clinical events increased as FFR decreased, and revascularization showed larger net benefit for lower baseline FFR values²⁴.

Furthermore, data from the FAME 2 trial also supports the notion that the benefit demonstrated in the percutaneous intervention (PCI) group may be related to the area of ischemia associated with the FFR value. The mean FFR value in both the medically treated and the PCI group was 0.68 in large epicardial arteries. The resultant large area of myocardium at risk may have contributed to the benefit demonstrated by treatment in the PCI group. This phenomenon is further highlighted when considering that the effects of PCI appeared to be more pronounced among patients who had lesions with an FFR of less than 0.65 than among patients who had only lesions with larger FFR values ($p < 0.01$). These findings support our conclusion that a significant level of ischemia (10-12.5%)¹⁴ corresponds with an FFR value of 0.64-0.67. However, just as in clinical practice an FFR of ≤ 0.80 is considered significant, so the extent of ischemia on CMR that is used to guide revascularization is often lower. A threshold of 5 % has been determined as significant in some trials^{2,25}. Interestingly, we show that 5 % ischemia corresponds exactly with an FFR value of 0.75 (Fig 2), thus again supporting the notion that as the FFR value increases, the CMR perfusion defect decreases. The debate as to what level of FFR and CMR ischemia is deemed significant will no doubt continue.

For FFR values less than 0.4, we observed a decrease in the extent of myocardial ischemia. This is unexpected and it is difficult to lay too much emphasis on this finding as the numbers are small. While we are unable to provide a clear understanding of this phenomenon it is interesting to postulate on the role of collaterals and pre-conditioning etc. The presence of collaterals may reduce the extent of ischemia in the region supplied by the artery with the lowest FFR. It has previously been demonstrated that coronary artery disease progression, as measured by quantitative coronary analysis is associated with an

increase in collateral supply whereas regression in disease is associated with reduced collateral formation²⁶.

As mentioned earlier, for FFR values in the range of 0.4- 0.5, the extent of ischemia was 25% in patients. This observation was the same in all three arteries and is similar to a recent 3D CMR perfusion study by Manka et al²⁷.

This study has a number of limitations. The sample size in this study is modest. However, this is the first study of this kind. Large sample sizes will be required to investigate how ischemic burden varies with lesion location and vessel size as alluded to earlier in the text. The matching of angiographic coronary arteries with territories on non-invasive imaging can never be exact. This could potentially lead to inaccuracies in assessment and allocation of ischemic burden. Additionally, assessing the relative contribution of two coronary arteries to one large area of perfusion defect involving adjacent territories is very subjective. For this study, qualitative visual assessment was used to reflect normal clinical practice. Fully quantitative perfusion analysis measuring absolute myocardial perfusion is slowly becoming available and may allow more accurate assessment of ischemic burden. However, since full quantification of perfusion by CMR is still a research tool within the validation stage we used a more established standard as the reference for this study. 3D perfusion may replace 2D perfusion as it allows for full coverage of the myocardium, which may further improve the quantification of ischemic burden²⁸. However, at this stage 3D imaging is not superior to 2D imaging and has a lower in-plane spatial resolution.

In conclusion, there is good correlation between FFR values and the extent of myocardial ischemia. FFR values above 0.75 are not associated with myocardial ischemia and ischemic burden increases linearly with smaller FFR values until a maximum ischemia of 25% is found in myocardium subtended by arteries with FFR values between 0.4 and 0.5. This information could potentially be used to target revascularization to a subgroup of patients with a positive FFR and high ischemic burden.

Conflict of Interest:

Prof Nagel received significant grant support from Bayer Schering Pharma and Philips Healthcare. Dr Chiribiri receives minor grant support from Philips Healthcare. The other authors declare that they have no competing interests

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Accepted Manuscript

References

1. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J* 2010;31:2501-2555.
2. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE, Investigators C. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;117:1283-1291.
3. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;107:2900-2907.
4. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF,

- Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-224.
- 5.** De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF, Investigators FT. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
- 6.** Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996;334:1703-1708.
- 7.** De Bruyne B, Pijls NH, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and animal validation. *Circulation* 2000;101:1840-1847.
- 8.** de Bruyne B, Bartunek J, Sys SU, Pijls NH, Heyndrickx GR, Wijns W. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation* 1996;94:1842-1849.
- 9.** Christian TF, Rettmann DW, Aletras AH, Liao SL, Taylor JL, Balaban RS, Arai AE. Absolute myocardial perfusion in canines measured by using dual-bolus first-pass MR imaging. *Radiology* 2004;232:677-684.
- 10.** Jerosch-Herold M, Swingen C, Seethamraju RT. Myocardial blood flow quantification with MRI by model-independent deconvolution. *Med Phys* 2002;29:886-897.

- 11.** Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 2007;115:1769-1776.
- 12.** Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettler K, Schonberg SO, Luchner A, Strohm O, Ahlstrom H, Dill T, Hoebel N, Simor T, Investigators M-I. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J* 2013;34:775-781.
- 13.** Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, Bijsterveld P, Ridgway JP, Radjenovic A, Dickinson CJ, Ball SG, Plein S. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012;379:453-460.
- 14.** Shaw LJ, Berman DS, Picard MH, Friedrich MG, Kwong RY, Stone GW, Senior R, Min JK, Hachamovitch R, Scherrer-Crosbie M, Mieres JH, Marwick TH, Phillips LM, Chaudhry FA, Pellikka PA, Slomka P, Arai AE, Iskandrian AE, Bateman TM, Heller GV, Miller TD, Nagel E, Goyal A, Borges-Neto S, Boden WE, Reynolds HR, Hochman JS, Maron DJ, Douglas PS, National Institutes of Health/National Heart L, Blood Institute-Sponsored ITI. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. *JACC Cardiovasc Imaging* 2014;7:593-604.

- 15.** Lockie T, Ishida M, Perera D, Chiribiri A, De Silva K, Kozerke S, Marber M, Nagel E, Rezavi R, Redwood S, Plein S. High-resolution magnetic resonance myocardial perfusion imaging at 3.0-Tesla to detect hemodynamically significant coronary stenoses as determined by fractional flow reserve. *J Am Coll Cardiol* 2011;57:70-75.
- 16.** Watkins S, McGeoch R, Lyne J, Steedman T, Good R, McLaughlin MJ, Cunningham T, Bezlyak V, Ford I, Dargie HJ, Oldroyd KG. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 2009;120:2207-2213.
- 17.** Costa MA, Shoemaker S, Futamatsu H, Klassen C, Angiolillo DJ, Nguyen M, Siuciak A, Gilmore P, Zenni MM, Guzman L, Bass TA, Wilke N. Quantitative magnetic resonance perfusion imaging detects anatomic and physiologic coronary artery disease as measured by coronary angiography and fractional flow reserve. *J Am Coll Cardiol* 2007;50:514-522.
- 18.** Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, Fleck E. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation* 2003;108:432-437.
- 19.** Ishida M, Schuster A, Morton G, Chiribiri A, Hussain S, Paul M, Merkle N, Steen H, Lossnitzer D, Schnackenburg B, Alfakih K, Plein S, Nagel E. Development of a universal dual-bolus injection scheme for the quantitative assessment of myocardial perfusion cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2011;13:28.
- 20.** Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS, American Heart Association Writing Group on Myocardial S, Registration for Cardiac I. Standardized

myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Int J Cardiovasc Imaging* 2002;18:539-542.

21. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol* 2012;59:1045-1057.

22. Leone AM, De Caterina AR, Basile E, Gardi A, Laezza D, Mazzari MA, Mongiardo R, Kharbanda R, Cuculi F, Porto I, Niccoli G, Burzotta F, Trani C, Banning AP, Rebuzzi AG, Crea F. Influence of the amount of myocardium subtended by a stenosis on fractional flow reserve. *Circ Cardiovasc Interv* 2013;6:29-36.

23. Yong AS, Ng AC, Brieger D, Lowe HC, Ng MK, Kritharides L. Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve. *Eur Heart J* 2011;32:345-353.

24. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Dominguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jimenez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, Lopez-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodes-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014;64:1641-1654.

25. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death:

differential stratification for risk of cardiac death and myocardial infarction.

Circulation 1998;97:535-543.

26. Berry C, Balachandran KP, L'Allier PL, Lesperance J, Bonan R, Oldroyd KG.

Importance of collateral circulation in coronary heart disease. *Eur Heart J*

2007;28:278-291.

27. Manka R, Paetsch I, Kozerke S, Moccetti M, Hoffmann R, Schroeder J, Reith S,

Schnackenburg B, Gaemperli O, Wissmann L, Wyss CA, Kaufmann PA, Corti R,

Boesiger P, Marx N, Luscher TF, Jahnke C. Whole-heart dynamic three-

dimensional magnetic resonance perfusion imaging for the detection of coronary

artery disease defined by fractional flow reserve: determination of volumetric

myocardial ischaemic burden and coronary lesion location. *Eur Heart J*

2012;33:2016-2024.

28. Jogiya R, Kozerke S, Morton G, De Silva K, Redwood S, Perera D, Nagel E,

Plein S. Validation of dynamic 3-dimensional whole heart magnetic resonance

myocardial perfusion imaging against fractional flow reserve for the detection of

significant coronary artery disease. *J Am Coll Cardiol* 2012;60:756-765.

Figure Title and Legend section:**Figure 1:** Scatter Plot of FFR values and % ischemia (All values)

The FFR values of each vessel have been plotted against the amount of ischemic myocardium subtended by that vessel. The unfilled dots represent the chronically occluded arteries which have been assigned a default value of 0.5.

Figure 2: Scatter plot between FFR values 0.4-0.8

Scatter plot of FFR values compared to ischemic burden of the corresponding vessel between the values of 0.4 and 0.8 demonstrating a linear relationship. The values for the occluded vessels have been removed and reference lines added to highlight the FFR values that correspond to the prognostically relevant ischemic burden threshold of 10 to 12.5%.

Figure 3: Scatter plot demonstrating the relationship between FFR value and percentage ischemia for the different coronary territories (too few points in the circumflex territory to allow a regression analysis)

Figure 4: Image of angiographic stenosis (a) and corresponding CMR images (b).

CMR perfusion images (Fig 4a) showing the apical, mid and basal slices with a lateral perfusion defect. The endocardial and epicardial borders are delineated (green), the perfusion defect is segmented (red) and calculated as percentage of the total myocardial area. In this case, the amount of ischemia measured is 21.5%.

Figure 4b shows the angiographic images with a significant lesion in the circumflex artery. The FFR value is 0.56.

Abbreviations CMR: Cardiovascular Magnetic Resonance

FFR: Fractional Flow Reserve

Table 1: Patient demographics and clinical characteristics (n=49)

Parameter	Number or mean $\pm$ standard deviation
Age (years)	61.9 $\pm$ 9.5
Men	37
Height (m)	1.71 $\pm$ 0.10
Weight (kg)	80.9 $\pm$ 14.7
Body Mass Index (kg/m ²)	27.8 $\pm$ 3.8
Diabetes Mellitus	15.7%
Hypertension	58.8%
Smoker	56.2%
Hypercholesterolemia	91.3%
Previous percutaneous intervention	12.0%
Previous myocardial infarction	7.8%
Canadian Class Symptoms	
1	5.9%
2	85.3%
3	8.8%
4	0
Drug therapy	
Aspirin	82.0%
Statin	71.4%
B blocker	60.0%
ACE I	30.0%

Table 2: Angiographic Characteristics (n=49)

Parameter	Number or mean $\pm$ standard deviation
No of FFR measurements (including occluded arteries)	59
Number of occluded arteries	8
Coronary artery with FFR >0.75	21
Coronary artery with FFR <0.75	38
Left anterior descending artery (including diagonal branch)	21
Circumflex artery (including marginal branches)	4
Right coronary artery	13
Patients with FFR positive results	
1- vessel disease	19
2- vessel disease	8
3-vessel disease	1
QCA in vessels with FFR $\leq$ 0.75 (% diameter stenosis)	49.8 $\pm$ 33.1
QCA in vessels with FFR >0.75 (% diameter stenosis)	85.0 $\pm$ 24.6

Table 3: Cardiovascular Magnetic Resonance perfusion imaging – Hemodynamic parameters (n=49)

Variable	
Heart Rate (bpm) Rest	64
Heart Rate (bpm) Stress	80
Systolic Blood Pressure (mmHg) Rest	136/77
Systolic Blood Pressure (mmHg) Stress	134/75
Heart Rate Pressure Product (bpm x mmHg) Rest	8704
Heart Rate Pressure Product (bpm x mmHg) Stress	10725

Table 4: Average ischemic area identified on Cardiovascular Magnetic Resonance perfusion imaging and Fractional Flow Reserve values per coronary territory and per Fractional Flow Reserve subgroup

Territory/FFR subgroup	Mean FFR value	Mean CMR value (%)
All arteries	0.67±0.17	8.92±9.35
All arteries (-occluded arteries)	0.69±0.17	8.39±9.49
Left anterior descending artery (All values)	0.71 ±0.15	8.01±9.3
Proximal Left anterior descending artery (n=7)	0.65± 0.11	10.3±8.77
Mid Left anterior descending artery (n=10)	0.68±0.20	8.1±10.4
Left anterior descending artery in 1 vessel disease (n=19)	0.71± 0.13	6.5± 8.7
Left anterior descending artery in 2-3 vessel disease (n=10)	0.71± 0.13	9.71±10.5
Right coronary artery	0.61 ±0.19	12.16±10.3
Circumflex artery	0.70 ±0.21	9.63±10.8
FFR value >0.75	0.81±0.07	0
FFR value 0.51-0.75	0.65±0.06	12.7±8.1
FFR value 0.4-0.5	0.46±0.02	23.02±1.53
FFR value <0.4	0.27±0.05	15.63±3.2

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