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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 ± 9.3%. An FFR value of ≥0.75 was not associated with ischemia on CMR. The maximum amount of ischemia (23.0±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±8.3%. In patients with 2 vessel disease (18%) the mean ischemic burden was 26.0±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 ischemia\textsuperscript{2,5}. 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 DSE\textsuperscript{6-8} and later against outcome\textsuperscript{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\textsuperscript{9,10}, outcome\textsuperscript{11} as well as in large prospective studies\textsuperscript{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 ischemia\textsuperscript{14}. Several studies have compared the diagnostic accuracy of CMR perfusion imaging and FFR\textsuperscript{15-17}. 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)\textsuperscript{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 bolus\textsuperscript{19} (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 classification\textsuperscript{20}. 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 >2mm 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 140μg 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 ±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 ± 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 ± 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 ± 9.0%; CX FFR 0.70 ± 0.21, CMR perfusion defect size 9.6 ± 10.7%; RCA FFR 0.61 ± 0.19, CMR perfusion defect size 12.2 ± 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 ± 8.78%; Mid LAD FFR 0.68 ± 0.20, CMR perfusion defect 8.1 ± 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±1.5%). For FFR values <0.4 less ischemia was found by CMR (mean value 15.6 ±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 stenosis. 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 ofperfused myocardium subtended by the stenosis. 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 demonstrated. 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 values.

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%) 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. 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 formation\textsuperscript{26}.

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 al\textsuperscript{27}.

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 burden\textsuperscript{28}. 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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differential stratification for risk of cardiac death and myocardial infarction. 


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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number or mean ± standard deviation</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>61.9 ± 9.5</td>
</tr>
<tr>
<td>Men</td>
<td>37</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.71 ± 0.10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.9 ± 14.7</td>
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<td>Body Mass Index (kg/m$^2$)</td>
<td>27.8 ± 3.8</td>
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<td>Diabetes Mellitus</td>
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<td>Hypertension</td>
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<td>Smoker</td>
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<td>Hypercholesterolemia</td>
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<td>Previous percutaneous intervention</td>
<td>12.0%</td>
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<tr>
<td>Previous myocardial infarction</td>
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<tr>
<td>Canadian Class Symptoms</td>
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</tr>
<tr>
<td>1</td>
<td>5.9%</td>
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<tr>
<td>2</td>
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<td>4</td>
<td>0</td>
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<td>Drug therapy</td>
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<td>Statin</td>
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<tr>
<td>B blocker</td>
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<tr>
<td>ACE I</td>
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Table 2: Angiographic Characteristics (n=49)

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<tbody>
<tr>
<td>No of FFR measurements (including occluded arteries)</td>
<td>59</td>
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<tr>
<td>Number of occluded arteries</td>
<td>8</td>
</tr>
<tr>
<td>Coronary artery with FFR &gt;0.75</td>
<td>21</td>
</tr>
<tr>
<td>Coronary artery with FFR &lt;0.75</td>
<td>38</td>
</tr>
<tr>
<td>Left anterior descending artery (including diagonal branch)</td>
<td>21</td>
</tr>
<tr>
<td>Circumflex artery (including marginal branches)</td>
<td>4</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>13</td>
</tr>
<tr>
<td>Patients with FFR positive results</td>
<td></td>
</tr>
<tr>
<td>1- vessel disease</td>
<td>19</td>
</tr>
<tr>
<td>2- vessel disease</td>
<td>8</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>1</td>
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<tr>
<td>QCA in vessels with FFR ≤0.75 (% diameter stenosis)</td>
<td>49.8 ± 33.1</td>
</tr>
<tr>
<td>QCA in vessels with FFR &gt;0.75 (% diameter stenosis)</td>
<td>85.0 ± 24.6</td>
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Table 3: Cardiovascular Magnetic Resonance perfusion imaging – Hemodynamic parameters (n=49)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Heart Rate (bpm) Rest</td>
<td>64</td>
</tr>
<tr>
<td>Heart Rate (bpm) Stress</td>
<td>80</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg) Rest</td>
<td>136/77</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg) Stress</td>
<td>134/75</td>
</tr>
<tr>
<td>Heart Rate Pressure Product (bpm x mmHg) Rest</td>
<td>8704</td>
</tr>
<tr>
<td>Heart Rate Pressure Product (bpm x mmHg) Stress</td>
<td>10725</td>
</tr>
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</table>
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

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