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# The Complementary Value of Absolute Coronary Flow in the Assessment of Patients with Ischaemic Heart Disease

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**Fractional flow reserve (FFR) is the current gold standard invasive assessment of coronary artery disease (CAD). FFR reports coronary blood flow (CBF) as a fraction of a hypothetical and unknown normal value. Although used routinely to diagnose CAD and guide treatment, how accurately FFR predicts actual CBF changes remains unknown. In this study, we compared fractional CBF with absolute CBF (aCBF, in ml min$^{-1}$), measured with a computational method during standard angiography and pressure wire assessment, on 203 diseased arteries (143 patients). We found a substantial correlation between the two measurements ($r = 0.89$ and Cohen's kappa $= 0.71$). Concordance between fractional and absolute CBF reduction was high when FFR was $>0.80$ (91%) but reduced when FFR was $\leq 0.80$ (81%), 0.70-0.80 (68%) and, particularly, 0.75-0.80 (62%). Discordance was associated with coronary microvascular resistance, vessel diameter and mass of myocardium subtended, all factors to which FFR is agnostic. Assessment of aCBF complements FFR and may be valuable to assess CBF, particularly in cases within the FFR 'gray zone'.**

Ischemic heart disease is caused by insufficient CBF to the myocardium. Because CBF cannot be measured directly in the cardiac catheter laboratory (CCL), cardiologists have relied largely upon sensor-tipped wire technologies (pressure, thermistor and Doppler) to derive several semi-quantitative indices, each serving as an indirect proxy for estimating CBF restriction[1]. Of these, pressure-derived FFR has emerged as the most popular and evidence-based method for guiding revascularization in intermediate lesions[2–4]. The value of FFR is that CBF restriction can be quantified, which allows revascularization to be targeted at lesions that restrict CBF the most. FFR is, however, a semi-quantitative assessment of fractional CBF reduction, unable to account for variability in vessel size (diameter), the mass of myocardium subtended and microvascular resistance (MVR), all of which influence aCBF. A 15% CBF reduction (FFR 0.85) due to a left main coronary artery stenosis is likely to result in a greater absolute reduction in myocardial blood flow over a larger myocardial territory, with potentially more serious clinical sequelae, than a 25% CBF reduction (FFR 0.75) resulting from disease in a smaller, more distal vessel. However, the opposite may be inferred by the FFR, and intervention may, therefore, not be targeted at the most physiologically significant lesion. Thus, a method that fully quantifies CBF changes, accounting for these important factors, may be of potential value. Methods for estimating aCBF in the CCL have been described[5–8]. In addition, these methods simultaneously measure absolute microvascular resistance (aMVR), thus resolving another limitation of FFR. Despite the popularity and importance of FFR in guiding key treatment decisions, the relationship between fractional and absolute CBF changes remains unknown, as does the potential value of these additional measurements when assessing patients for intervention. In this study of aCBF, we investigated (1) the relationship between fractional (FFR) and absolute CBF changes and (2) concordance and discordance between fractional and absolute CBF changes.

## Results

**Case exclusions and software failures.** In total, 256 arteries from 169 patients met the inclusion criteria and were recruited. Of these, 20 arteries had insufficient pressure gradient for determining aCBF, and 19 had inadequate angiographic views for modeling, leaving 217 suitable cases. Of these, seven failed to mesh, and seven failed to converge during numerical simulation. The final analysis included 203 arteries from 143 patients. Therefore, of those cases meeting the clinical inclusion criteria, the computational fluid dynamics (CFD) method computed physiological results successfully in 93.5% of cases. A software problem resulted in vessel diameter data being unavailable in 28 cases.

**Baseline patient and vessel characteristics.** The baseline demographic and clinical characteristics of all 143 patients are shown in Table 1. Artery-specific and lesion-specific characteristics are summarized in Table 2. Overall, 51% of arteries underwent percutaneous coronary intervention (PCI), and 49% were treated medically. Ninety-three percent of arteries with a positive FFR ($\leq 0.80$) underwent PCI, and 7% were treated with medical therapy, whereas 2% of cases with a negative FFR ($>0.80$) underwent PCI, and 98% were treated medically. Median hyperemic aCBF, coronary flow reserve (CFR) and MVR were 85.2 (63.5–116.3 ml min$^{-1}$), 1.62 (1.32–2.04) and 0.71 (0.52–0.98 mmHg.min/ml), respectively. The aCBF was higher in the left main stem (LMS), left anterior descending artery (LAD) and right coronary artery (RCA) cases (95.6 ml min$^{-1}$, 81.6 ml min$^{-1}$ and 98.8 ml min$^{-1}$, respectively) than the left circumflex artery (LCX), diagonal and obtuse marginal (OM) cases (78.1 ml min$^{-1}$, 79.9 ml min$^{-1}$ and 56.7 ml min$^{-1}$, respectively), but these differences did not reach statistical significance.

**Reduction in aCBF.** The median reduction in aCBF (from hypothetical normal, caused by epicardial disease) was 20.6 (12.4–38.3)

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**Table 1 | Baseline patient characteristics**

| Characteristic | Study population ($n=143$) $n$ (%), mean $\pm$ s.d. or median (IQR) |
|---|---|
| **Demographic characteristics** | |
| Mean age (years) | $65\pm10$ |
| Male | 108 (75.5) |
| White British | 128 (89.5) |
| Current tobacco use | 21 (14.7) |
| Previous tobacco use | 70 (49) |
| **Common diagnoses** | |
| Previous MI | 36 (25.2) |
| Hypertension | 93 (65) |
| Hyperlipidemia | 108 (75.5) |
| Diabetes mellitus | 37 (25.9) |
| Obesity | 39 (27.3) |
| COPD | 10 (7) |
| Asthma | 4 (2.8) |
| Peripheral vascular disease | 4 (2.8) |
| Atrial fibrillation | 5 (3.5) |
| Valvular heart disease | 7 (5) |
| LVEF <50% | 29 (20.3) |
| **Hematology and biochemistry** | |
| eGFR (ml/min/1.73 m$^2$) | 82 (66–90) |
| Hemoglobin (g dl$^{-1}$) | $141.3\pm14.6$ |

MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

ml min$^{-1}$. FFR-positive cases were associated with a greater reduction in aCBF than FFR-negative cases (34.6 versus 11.6 ml min$^{-1}$, $P<0.0001$). The threshold for significance for reduction in aCBF was determined as a reduction in aCBF of $\geq23$ ml min$^{-1}$. Reduction in aCBF was numerically but statistically non-significantly higher in LMS, LAD and RCA cases (median values: 45.7 ml min$^{-1}$, 21.1 ml min$^{-1}$ and 23.7 ml min$^{-1}$, respectively) compared to LCX, diagonal and OM branch cases (median values: 20.8 ml min$^{-1}$, 17.8 ml min$^{-1}$ and 12.8 ml min$^{-1}$, respectively).

**Relationship between fractional and absolute flow reduction.** Fractional CBF reduction (measured by FFR) was plotted against aCBF reduction (measured by the CFD method). Despite a strong correlation between fractional and absolute CBF reduction ($r=0.89$ and 0.86–0.92, $P<0.001$), there was variability among individual cases (Fig. 1). When the cases were divided into those with significant or non-significant CBF reduction according to FFR (fractional reduction) and according to aCBF (absolute reduction), the Cohen's kappa statistic was 0.71, indicating a substantial agreement between the two parameters.

**Concordance between fractional and absolute flow reduction.** All 203 cases were categorized as physiologically concordant (significant FFR and significant aCBF reduction or non-significant FFR and non-significant aCBF reduction) and discordant. Discordance between fractional and absolute CBF reduction was low in FFR-negative (FFR >0.80) cases (9%). Discordance was significantly higher in FFR-positive cases (19%, $P<0.05$), higher still when FFR was between 0.70 and 0.80 (32%, $P<0.01$) and highest when FFR was in the 0.75–0.80 'gray zone' (38%, $P<0.01$). Discordance was 0% in cases with FFR <0.70 (Fig. 1).

**Factors affecting discordance.** When comparing the fractional and absolute reduction in CBF, differences in coronary MVR, vessel diameter and myocardial jeopardy were identified that were associated with discordance between these two measures (Fig. 2). In cases with FFR $\leq0.80$, aMVR was significantly higher (causing reduced aCBF) in discordant cases than concordant cases (1.02 versus 0.51 mmHg.min/ml, $P<0.01$). The same was true of the FFR 0.70–0.80 and 0.75–0.80 groups (1.02 versus 0.57 mmHg.min/ml and 1.00 versus 0.55 mmHg.min/ml, respectively, $P<0.01$ for both comparisons). In cases with FFR >0.80, aMVR was significantly lower (causing higher CBF) in discordant cases than concordant cases (0.57 versus 0.84 mmHg.min/ml, $P<0.01$) (causing increased CBF). Myocardial jeopardy was consistently and significantly lower in discordant cases than concordant cases in all cases with FFR $\leq0.80$ (7.28 versus 5.28, $P<0.05$), in those with FFR 0.70–0.80 (7.69 versus 5.28, $P<0.05$) and in those with FFR 0.75–0.80 (8.27 versus 5.21, $P<0.05$). In cases with FFR >0.80, myocardial jeopardy was numerically higher in discordant cases, but this difference did not reach statistical significance (7.71 versus 5.69, $P=$ not significant (NS)). Vessel diameter was significantly greater in concordant than discordant in cases with FFR 0.70–0.80 and in those with FFR 0.75–0.80 (3.33 versus 2.85 mm, $P<0.05$, and 3.51 versus 2.92 mm, $P<0.05$). In cases with FFR >0.80 and in those with FFR $\leq0.80$, no significant difference was observed in vessel reference diameter between concordant and discordant cases (2.92 versus 2.81 mm, $P=$ NS, and 3.14 versus 2.85 mm, $P=$ NS). Thus, heterogeneity in aMVR, myocardial jeopardy and vessel size appeared to contribute to discordance between fractional and absolute CBF reduction.

**Discussion**

The main findings of this study were that there was a substantial correlation between fractional and absolute flow reduction, but that individual case variation resulted in discordance in 9% of cases with a physiologically non-significant FFR and 19% of those with a physiologically significant FFR. Discordance was greatest in cases within the FFR 'gray zone' where it reached 38%. Discordance between fractional and absolute CBF reduction appeared to be associated with variability in three related factors: coronary MVR, myocardial jeopardy (a marker of mass of myocardium subtended) and vessel size.

The ability to fully quantify aCBF changes may extend the benefits currently provided by FFR. It would be reasonable to infer that a lesion that reduces CBF by 50 ml min$^{-1}$ is more likely to cause symptoms and clinical sequelae than a lesion that reduces CBF by 10 ml min$^{-1}$. FFR is effectively normalized for vessel size but is agnostic to differences in absolute flow. Whether symptoms and clinical sequelae are better predicted by the absolute or the fractional flow reduction remains unknown. This was not the subject of this study. Rather, this study demonstrated that there was variability between absolute and fractional CBF reduction. In the current study, disparity between fractional and absolute CBF reduction was associated with changes in three related factors: vessel size (diameter), myocardial resistance and the mass of myocardium subtended by that artery. FFR does not account for these parameters, all of which are important determinants of CBF. Instead, in real-world practice, the operator assesses these factors automatically by 'eye-balling' the angiogram. Similar relationships have been demonstrated previously with CFR and the index of microcirculatory resistance (IMR). Variability in IMR accounts for discordance between FFR and Doppler-derived CFR[9,10].

The novel method also predicted aMVR, which may be advantageous for several reasons. First, naturally occurring and pathological variability in aMVR is known to explain discordance between pressure-based and flow-based intracoronary assessment[10,11]. Second, MVR assessment is helpful in the diagnosis of coronary microvascular disease and is now supported by a 2A recommendation in the European Society of Cardiology guidelines[12]. Microvascular disease

**Table 2 | Vessel and lesion characteristics**

| Artery | n (%) | FFR median (IQR) | FFR ≤0.80 n (%) | Average % stenosis | Ischemic burden (myocardial jeopardy) |
|---|---|---|---|---|---|
| Left anterior descending | 103 (50.7) | 0.79 (0.71–0.85) | 58 (56.3) | 59% | 6.5 |
| Right coronary | 45 (22.2) | 0.80 (0.63–0.88) | 25 (55.6) | 66% | 7.6 |
| Left circumflex | 26 (12.8) | 0.80 (0.71–0.87) | 14 (53.8) | 64% | 4.6 |
| Diagonal | 17 (8.4) | 0.82 (0.79–0.86) | 7 (41.2) | 53% | 5.1 |
| Obtuse marginal | 7 (3.4) | 0.87 (0.79–0.93) | 2 (28.6) | 58% | 3.7 |
| Left main | 5 (2.5) | 0.76 (0.65–0.79) | 3 (60) | 63% | 13.4 |
| Total | 203 | 0.80 (0.72–0.87) | 109 | 61% | 6.4 |

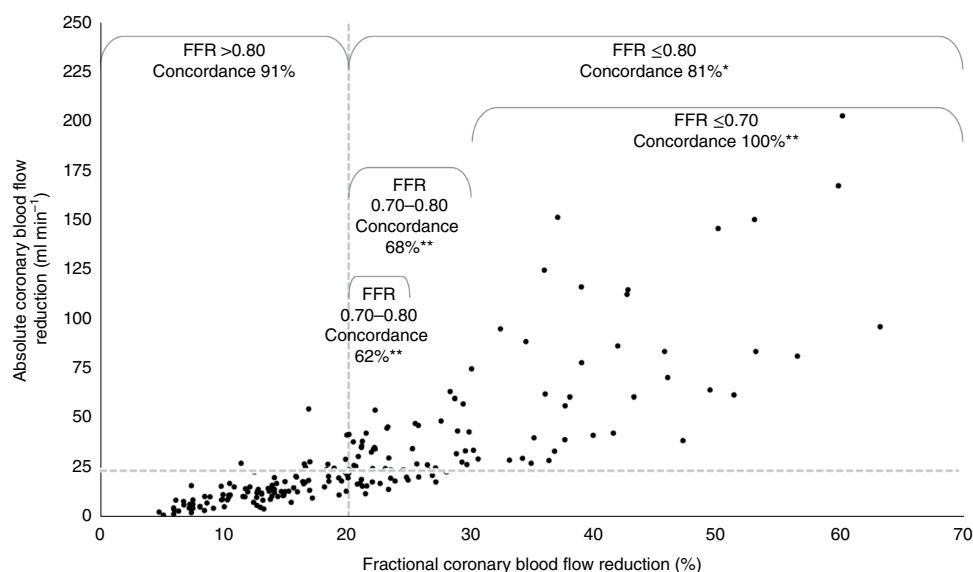Ischemic burden indicates the vessel-specific myocardial jeopardy score.



**Fig. 1 | The relationship between fractional and absolute CBF reduction.** Concordance between fractional and absolute CBF reduction is indicated by the labels according to the FFR range. Concordance means significant FFR (≤0.80) and significant reduction in aCBF (≥23 ml min⁻¹) or insignificant FFR (>0.80) and insignificant reduction in aCBF (<23 ml min⁻¹). The horizontal and leftward vertical dashed lines reflect the thresholds for physiological significance for FFR and aCBF. The asterisks indicate statistical significance for differences in concordance (z-scores) compared to the FFR >0.80 group at the *$P < 0.05$ and **$P < 0.01$** levels (exact $P$ values (two-tailed) were 0.021 for the ≤0.80 group, <0.001 for the 0.70–0.80 and 0.75–0.80 groups and 0.02 for the ≤0.70 group, unadjusted for multiple comparisons). There were no replicates.

responds to medical therapy but is rarely diagnosed in the CCL because standard tests, such as FFR, cannot identify or measure it[13]. Third, it has been suggested that concomitant microvascular dysfunction may be one reason why 20% of patients do not achieve full symptomatic relief with PCI, even when FFR-guided[4]. It is, therefore, interesting that the rate of discordance in FFR-'positive' patients in our study was similar at 19%.

FFR was least reliable at predicting aCBF changes in cases with FFR 0.70–0.80 (68% concordance) and poorest in the range 0.75–0.80 (62% concordance). This is interesting because this FFR range corresponds with what has become known as the FFR 'gray zone'. The DEFER trial originally proposed FFR >0.75 as the threshold for deferring intervention in favor of medical therapy[14], whereas the seminal FAME and FAME-2 trials supported a threshold of FFR >0.80 (refs. [15,16]). The higher threshold increases the sensitivity for detecting flow-limiting lesions but comes at the expense of reducing specificity. It is, therefore, interesting that the current study identified those with an FFR in the same range as being most discordant with aCBF.

The values of aCBF reduction are lower than those reported for the continuous infusion thermodilution (CIT) method[17]. There are two main reasons for this. First, our population had hemodynamically

significant epicardial coronary artery disease, whereas data supporting the CIT method are largely derived from those with unobstructed coronary arteries. Second, the novel CFD method determines the coronary outlet flow, whereas CIT predicts inlet flow, the former being much greater due to the loss of flow to side branches, particularly in the LAD, which supplies multiple branches to the lateral wall and septum. Outlet flow is a lesion-specific parameter that allows the reduction in CBF due to proximal disease to be derived, which may be useful when predicting the physiological value of PCI and making revascularization decisions. Finally, the two methods are distinct, and a systematic or methodological influence cannot be excluded.

The methods used in this study do not compete with or invalidate FFR. Quite the opposite is true. FFR predicts CBF as a fraction of an hypothetical and unknown value. The novel method translates this into a value, converting a semi-quantitative into a fully-quantitative measurement. Moreover, the novel method requires the data acquired during FFR and the mathematics used in its derivation. In this way, the two methods may be complementary. Given that agreement between FFR-predicted flow reduction and aCBF reduction was high in cases where FFR was >0.80 and perfect when FFR was
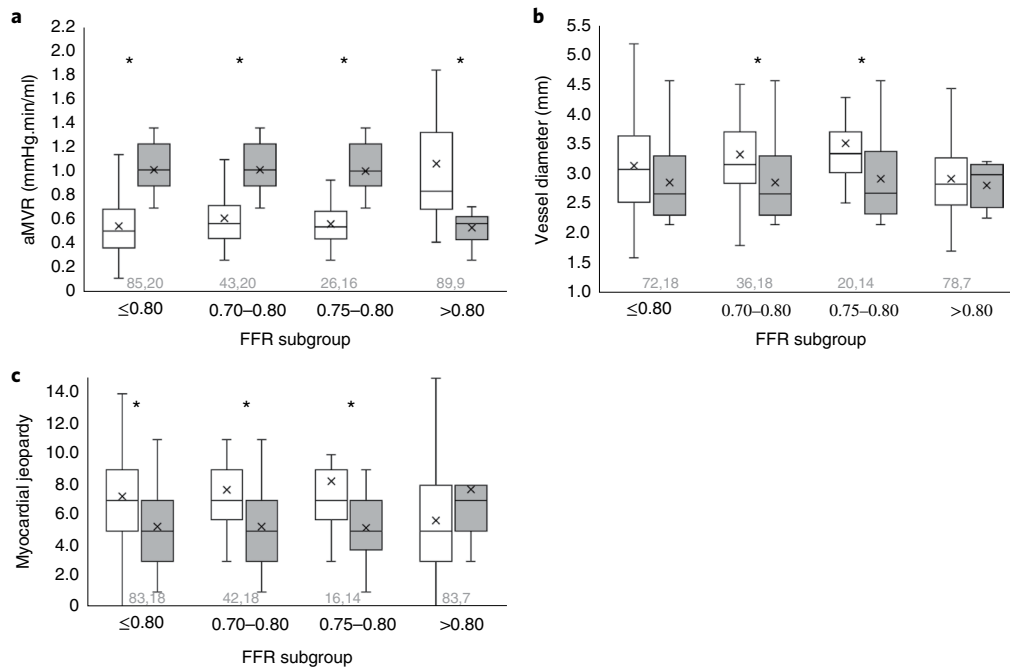
**Fig. 2 | Factors affecting discordance.** Box and whisker plots demonstrating the difference between concordant (white boxes) and discordant (shaded boxes) cases in each FFR subgroup on the basis of aMVR (**a**), vessel diameter (**b**) and myocardial jeopardy (**c**). The direction of these differences is associated with discordance between absolute and fractional coronary blood flow changes. Concordance was 100% in the FFR <0.70 group, hence the absence of a plot for this subgroup. The box defines the IQR; the line and 'x' indicate the median and mean; and the bars represent variability outside the upper and lower quartiles, excluding outliers. Asterisks indicate statistical significance at the $P \leq 0.05$ level ($P$ values for **a** are all <0.001; $P$ values for **b** are 0.03 and 0.02; and $P$ values for **c** are 0.018, 0.019 and 0.021—calculated in Rstudio (two-sided Mann–Whitney $U$-test) with no adjustment for multiple comparisons). The numbers in gray indicate $n$ for each group in each comparison (no replicates).

≤0.70, a hybrid approach to coronary assessment may have value, with assessment of aCBF being required only if the FFR value lay in the range of 0.70–0.80. If this approach were applied to the current dataset, FFR alone would be sufficient in 65% of cases, and additional assessment of aCBF would be required in 35%.

The study was observational, and so the results are hypothesis generating. The clinical benefits of assessing CBF reduction in absolute terms are yet to be proven. The application of the proposed hybrid assessment is hypothetical. Currently, the CFD method does not account for flow to side branches, which underestimates flow in the proximal vessel. The novel method awaits in vivo validation but has been tested in vitro, in unbranched phantom models. It requires a pressure gradient of at least 4 mmHg, which roughly equates to a trans-lesional pressure ratio of 0.95. The latter means that, at the current stage of development, the method cannot be used in clearly unobstructed epicardial coronary arteries, which is a limitation in patients under investigation for ischemia with no obstructive coronary disease. Due to an error in the software, vessel diameter data were unavailable in 28 cases (13.7%).

## Conclusions
In patients with CAD, a substantial correlation was observed between (pressure-derived) fractional and (computed) aCBF reduction. Concordance between fractional and absolute flow reduction was high when FFR was >0.80 and <0.70 but was poorer when 0.70–0.80 and poorest in the 0.75–0.85 'gray zone' range. Assessment of aCBF reduction may complement FFR and extend its benefits in selected cases.

## Methods
**Patient inclusion and exclusion criteria.** This study was approved by the South Yorkshire Health Research Authority Regional Ethics Committee

(16/NW/0897 and 08/H1308/193). Patients were eligible for inclusion if they were being investigated for chest pain by invasive coronary angiography and pressure wire assessment, were aged 18 years or older and provided informed consent where appropriate. Participants were not compensated for inclusion and were recruited from elective and inpatient cardiac catheter lists at Sheffield Teaching Hospitals NHS Foundation Trust. Only cases suitable for pressure wire assessment were included, and so results may not be representative in other cases. Patients with chronic and acute coronary syndromes were included, but, in acute cases, only non-culprit arteries were studied. Patients with ST-segment elevation myocardial infarction within 60 days, contraindication to adenosine or contrast media, previous coronary artery bypass surgery, chronic total occlusion, severe valvular disease, inability to consent or without angiographically significant CAD were excluded. The clinical data of all patients are reported in Supplementary Dataset 1.

**Angiographic and pressure wire data collection.** Invasive coronary angiography was performed according to standard clinical protocols. Operators were encouraged to optimize target artery opacification, acquire clear views of the stenosis region and minimize vessel overlap and panning to facilitate arterial reconstruction[18]. A panel of three cardiologists, independent of physiological simulation, evaluated each angiogram to assess the reconstruction. Each panel member had to be satisfied for a case to be included. The panel also assessed global and vessel-specific myocardial ischemic jeopardy index and the percentage lesion stenosis for all cases. The myocardial jeopardy index is a lesion-specific measure of the number of myocardial segments jeopardized by a stenosis and is, therefore, a marker of the mass of myocardium subtended[19]. Pressure wire assessment also proceeded according to standard protocols with trans-lesional pressure measurements acquired under baseline and hyperemic conditions. Hyperemia was induced with an intravenous infusion of adenosine (140 mcg/kg/min)[20]. The method for deriving aCBF (detailed below) uses data from angiography and a 0.014-inch pressure wire. In this study, the PressureWire X (Abbott Laboratories) and PrimeWire Prestige (Philips Volcano) were used. Any lesion with FFR ≤0.80 was regarded as physiologically significant and treated accordingly. FFR reports CBF as the fraction of CBF that remains, in an epicardial coronary artery, relative to an hypothetical normal value for that artery, under maximal flow conditions. Fractional (percentage) reduction in flow was, therefore, calculated as $1 - \text{FFR}$, multiplied by 100. The hemodynamic data are included in Supplementary Dataset 2.

**Deriving absolute coronary flow and absolute coronary microvascular resistance.** aCBF was computed by the CFD model. Three-dimensional (3D) coronary arterial anatomy was reconstructed from two angiographic projections ≥30° apart, acquired during ECG-gated end diastole, using an epipolar line transaction method[21]. The panel of cardiologists assessed all arterial reconstructions and models against the angiographic images to ensure that each reconstructed model was based on the artery in question. The reconstructed arterial volume was discretized; measured pressures were applied as boundary conditions; and a numerical simulation based upon solving the 3D, incompressible Navier–Stokes and continuity equations was performed. The principal model output was a calculation of aCBF, distal to the epicardial stenosis/es, at the location of the pressure wire transducer. A detailed description of the method was previously published[5]. Only cases with FFR ≤0.95 or ≥4 mmHg trans-lesional pressure gradient were included because an insufficient pressure gradient is associated with increased model error. By combining measurements of aCBF and pressure, aMVR and the reduction in aCBF due to epicardial disease were also calculated. aMVR (mmHg.min/ml) was calculated according to the hydraulic equivalent of Ohm's law, as the ratio of distal pressure ($P_d$) and aCBF ($\frac{P_d}{aCBF}$). The aCBF in the hypothetical non-stenosed artery was calculated as the ratio of aCBF and FFR ($\frac{aCBF}{FFR}$), and the reduction in aCBF due to epicardial coronary disease was calculated as the difference between this and aCBF. These physiological parameters were calculated on a vessel-specific basis under baseline and hyperemic conditions.

The primary outcome was to assess the relationship (correlation, concordance and discordance) between fractional (FFR) CBF reduction and absolute CBF reduction in a population of patients with CAD. A subgroup analysis was also performed according to clinically relevant ranges of FFR (≤0.80, 0.70–0.80, 0.75–0.80 and ≤0.70). Simulations were performed on a Dell Precision T5600 computer (Intel Xeon E5 2560, 2-GHz processor, 32 GB RAM) or a Dell Precision 5540 mobile workstation (Intel Core i9-9980HK processor, 32 GB RAM).

**Statistical analysis.** Statistical analysis was performed in RStudio 1.2.1335 (R, version 3.6.1) and in Microsoft Excel (16.16.27). Normality of distribution was assessed with histograms, Q–Q plots and the Shapiro–Wilk test. Parametric and non-parametric continuous data are presented as mean (±s.d.) and median (interquartile range (IQR)), respectively. Wilcoxon signed-rank and Mann–Whitney $U$-tests were used to compare paired and unpaired grouped data. Levene's test for homoscedasticity was used, and we found evidence of heteroscedasticity. Therefore, the Kruskal–Wallis test was used to compare groups of data (rather than a standard ANOVA). Proportions were compared by calculating the z-score. To determine the threshold for significance for aCBF reduction, a power regression model ($y = a \cdot x^b$) was applied to absolute CBF and fractional CBF reduction ($1 - FFR$), which were plotted against each other, at a point equivalent to FFR = 0.80. Correlation between aCBF and percentage flow reduction was assessed with Pearson's correlation coefficient ($r$) after log-transformation for continuous data and with Cohen's kappa correlation coefficient ($\kappa$) for categorical data (concordance and discordance), which adjusts for agreement expected by chance and is a number between −1.0 and 1.0, with values of 0, 0.10–0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, 0.81–0.90 and 1.0, indicating none (equivalent to chance), slight, fair, moderate, substantial, near-perfect and perfect agreement, respectively[22]. Negative values indicate agreement worse than that expected by chance. To detect a 15% reduction in concordance (α = 0.05) with 80% power, we required around 50 cases in each subgroup. We aimed to include 200 cases in total, to ensure ≥50 in the major subgroup comparisons (FFR-positive versus FFR-negative and versus 0.70–0.80). $P$ values were not corrected for type 1 error (alpha) for multiple comparisons.

**Reporting summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

## Data availability

All the data supporting the findings in this research letter are provided as source data and supplementary information to this manuscript.

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## Author contributions

P.D.M. and J.P.G. conceived the original idea for the study and collected the clinical data. D.R.H., I.H., P.V.L. and A.N. supported software development and modeling. L.A.-R. performed the physiological simulations, supported by T.N. and D.T. L.A.-R. led the statistical analysis. All authors were involved in drafting the manuscript.

## Competing interests

The authors have no financial conflicts of interest. P.D.M., J.P.G., P.J.L. and D.R.H. are named as inventors on a University of Sheffield patent application describing the CFD method ('VIRTU-Q: a method for determining volumetric blood flow'; patent application no. 1813170.6).

## Additional information

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| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. $F$, $t$, $r$) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted <br> *Give P values as exact values whenever suitable.* |
| ☒ | ☐ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ | Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated |

*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| Data collection | No software were used for data collection. Proprietary software were used to process the results as described in the manuscript. |
|---|---|
| Data analysis | No software were used for data collection. Proprietary software were used to process the results as described in the manuscript. From the manuscript: statistical analysis was performed in RStudio 1.2.1335 (R, v3.6.1). |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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We have made underlying data available in the supporting material and have added a sentence stating this in the manuscript

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# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Sample size | To detect a 15% reduction in concordance (α 0.05) with 80% power, we required around 50 cases in each subgroup. We aimed to include 200 cases in total, to ensure ≥50 in the major sub-group comparisons (FFR positive vs negative and vs 0.70-0.80). |
| Data exclusions | The clinical case exclusions are well described in the manuscript: Case exclusions and software success. Two hundred and fifty-six arteries from 169 patients met the inclusion criteria and were recruited. Of these, 20 arteries had insufficient pressure gradient for determining aCBF and 19 had inadequate angiographic views for modelling, leaving 217 suitable cases. Of these, seven failed to 'mesh' and seven failed to 'converge' during numerical simulation. 203 arteries from 143 patients were included in the final analysis. Therefore, of those cases meeting the clinical inclusion criteria, the novel method computed a result successfully in 93.5% of cases. |
| Replication | This was a comparison of FFR versus abs flow. There was no replication, because these were clinical observations. |
| Randomization | NA: there was no allocation to experimental or control groups in this study and so no randomisation. |
| Blinding | There was no allocation to any experimental grouping. As described in th manuscript, the only blinding involved the panel of cardiologists who analysed the myocardial jeopardy score did so blinded to the absolute flow and microvascular results. |

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☒ | Antibodies |
| ☒ | Eukaryotic cell lines |
| ☒ | Palaeontology and archaeology |
| ☒ | Animals and other organisms |
| ☐ | ☒ Human research participants |
| ☒ | Clinical data |
| ☒ | Dual use research of concern |

### Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ChIP-seq |
| ☒ | Flow cytometry |
| ☒ | MRI-based neuroimaging |

# Human research participants

| | |
|---|---|
| Population characteristics | From the manuscript: Baseline patient and vessel characteristics. The baseline demographic and clinical characteristics of all 143 patients are shown in Table 1. Artery- and lesion-specific characteristics are summarised in Table 2. Overall, 53% of arteries underwent PCI and 47% were treated medically. Ninety-three percent of arteries with a positive FFR ($\leq$0.80) underwent PCI and seven percent were treated with medical therapy, whereas two percent of cases with a negative FFR (>0.80) underwent PCI and 98% were treated medically. |
| Recruitment | From the manuscript: Patients were eligible for inclusion if they were being investigated for chest pain by invasive coronary angiography and pressure wire assessment, were aged 18 years or older and provided informed consent where appropriate. Participants were not compensated for inclusion and were recruited from elective and inpatient cardiac catheter lists at Sheffield Teaching Hospitals NHS Foundation Trust. Only cases suitable for pressure-wire assessment were included and so results may not be representative in other cases. Patients with chronic and acute coronary syndromes were included but, in acute cases only non-culprit arteries were studied. Patients with ST-segment elevation myocardial infarction within 60 days, contraindication to adenosine or contrast media, previous coronary artery bypass surgery, chronic total occlusion, severe valvular disease, inability to consent or without angiographically significant coronary artery disease were excluded. |
| Ethics oversight | From the manuscript: The study was approved by the South Yorkshire Health Research Authority Regional Ethics Committee (16/NW/0897 and 08/H1308/193). A statement regarding informed consent is included in the manuscript. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.