Assessment of multi-vessel coronary artery disease using cardiovascular magnetic resonance pixelwise quantitative perfusion mapping

Brief Title: CMR perfusion mapping for assessment multi-vessel coronary disease

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ABSTRACT

Background
Visual assessment (VA) of first-pass stress perfusion cardiovascular magnetic resonance (CMR) may underestimate ischaemia in multivessel coronary artery disease (MVCAD). Pixelwise perfusion mapping allows quantitative measurement of regional myocardial blood flow (MBF) which may improve ischaemia detection in MVCAD.

Objectives
To compare the diagnostic accuracy of quantitative perfusion maps to VA of first-pass perfusion images for the detection of MVCAD.

Methods
One hundred and fifty-one subjects recruited at two centres underwent stress perfusion CMR with myocardial perfusion mapping and invasive coronary angiography with coronary physiology assessment. Ischaemic burden was assessed by VA of first-pass images and by quantitative measurement of stress MBF using perfusion maps.

Results
In patients with MVCAD (two-(2VD) or three-vessel disease (3VD), n=95), perfusion mapping identified significantly more segments with perfusion defects (segments per patient 12 (9-16) by mapping vs 8 (5-9.5) by VA, $p<0.001$). Ischaemic burden (IB) measured using mapping was higher in MVCAD compared to IB measured using VA (3VD: mapping 100% (75-100%) vs first-pass 56% (38-81%); 2VD: mapping 63% (50-75%) vs first-pass 41% (31-50%); both $p<0.001$) but there was no difference in single-vessel disease (mapping 25% (13-44%) vs 25% (13-31%)). Perfusion mapping was superior to VA for the correct identification of extent of coronary disease (78% vs 58%, $p<0.001$) due to better identification of 3VD (87% vs 40%) and 2VD (71% vs 48%).

Conclusion
VA of first-pass stress perfusion underestimates ischaemic burden in MVCAD. Pixelwise quantitative perfusion mapping increases the accuracy of CMR in correctly identifying extent of coronary disease. This has important implications for assessment of ischaemia and therapeutic decision making.

KEYWORDS: Cardiovascular magnetic resonance, myocardial blood flow, adenosine stress, coronary artery disease

ABBREVIATIONS:

2VD: two-vessel disease

3VD: three-vessel disease

CAD: Coronary artery disease

CMR: Cardiovascular magnetic resonance

FFR: Fractional flow reserve

MBF: Myocardial blood flow

MVCAD: Multivessel coronary artery disease

PCI: Percutaneous coronary intervention

INTRODUCTION

Multivessel coronary artery disease (two- or three-vessel obstructive disease, MVCAD) is found in approximately 30% of patients undergoing elective coronary angiography(1). When managed medically, patients with MVCAD have a poorer outcome (12-year survival 40% for three-vessel disease (3VD) and 59% for two-vessel disease (2VD)) compared to those with single-vessel disease (12-year survival 74%)(2).

Stress perfusion CMR is a highly accurate tool for the detection of obstructive coronary artery disease (CAD)(3,4) but it has been suggested that CMR may underestimate the burden of ischaemia in patients with MVCAD(5,6). It has previously been shown that perfusion defects in all three coronary territories are only present in up to 58% of patients with known obstructive 3VD(7).

With the increasing use of stress perfusion CMR to guide revascularization strategies, it is essential to correctly identify all areas of ischaemia. In patients with MVCAD, when first-pass stress perfusion images are analyzed visually, perfusion defects are often most prominent in one coronary territory, usually the one with the most severe coronary stenosis, and defects in other territories may be subtler or appear to be absent. Quantitative myocardial perfusion mapping is a novel tool for the assessment of ischaemia, allowing for rapid quantification of myocardial blood flow (MBF) using automatically generated pixel-wise myocardial perfusion maps(8). This sequence has been recently validated for the detection of obstructive CAD with a regional stress MBF value <1.94ml/g/min defined as the threshold for ischaemia(9). Others have also demonstrated the accuracy of quantitative MBF measurements using CMR(10,11). Positron-emission tomography (PET) quantification of MBF has been available for many years now and has shown potential benefit in the detection of MVCAD (overcoming balanced ischaemia) and in the assessment of microvascular dysfunction(12) The ability to measure MBF at a regional level may improve the accuracy of

diagnosis of MVCAD by CMR and provide a useful tool for the assessment of ischaemic burden but this requires further assessment.

We hypothesized that measurement of stress MBF using myocardial perfusion maps would improve the detection of ischemia in MVCAD and increase the diagnostic accuracy of CMR in the identification of MVCAD versus single-vessel disease.

METHODS

Study population

A total of 151 patients from two centers (95 from Royal Free Hospital, London, UK and 56 from Barts Heart Centre, London, UK) undergoing clinically indicated stress perfusion CMR were retrospectively identified. All had undergone coronary angiography for investigation of suspected CAD within 6 months of the stress perfusion CMR scan. At coronary angiography, a stenosis was assessed as significant if angiographic diameter stenosis was >90% by visual assessment (VA) or if fractional flow reserve (FFR) was <0.80 in the presence of angiographic diameter stenosis 50-90%. Diameter stenosis <50% was considered non-significant(13). The presence of a chronic total occlusion (CTO) precluded measurement of FFR in any vessel providing collateral flow due to overestimation of FFR in this circumstance(14). In this situation, angiographic assessment alone was used, with >70% diameter stenosis deemed significant. Ninety-five consecutive patients with MVCAD (47 with 2VD and 48 with 3VD) were included. Additionally, we selected 31 consecutive patients with obstructive single-vessel disease and 25 with no obstructive disease (defined as angiographic diameter stenosis <50% or FFR <0.80 in all major epicardial vessels) undergoing stress perfusion CMR for analysis of myocardial ischaemic burden.

Exclusion criteria were standard contra-indications to CMR, adenosine or gadolinium contrast, and patients who had undergone angioplasty (PCI) in the six months prior to the

CMR scan (unless repeat angiography was performed within 6 months after the CMR scan in which case data from the second angiogram was used for analysis).

All participants underwent investigations for clinical reasons and provided written informed consent for use of their data for research purposes. Approval was provided by the University College London/University College London Hospital Joint Committees on the Ethics of Human Research for recruitment at Royal Free Hospital (REC reference 07/H0715/101) and East of England Research Ethics Committee for Barts Heart Centre (REC reference 14/EE/0007). CMR data acquisition used a research sequence and image reconstruction software provided by the National Institutes for Health (NIH) under a core-competency partnership (C2P) agreement with Siemens which stipulates that local institutional approval is required for use in diagnostic clinical studies. This approval was given by the Director of CMR Imaging and the Clinical Director of Imaging at Barts Heart Centre who oversee governance for CMR at both recruiting sites. This is an established process which validates that patient safety guidelines are met and that the use of research methods is in the best interest of the patient as determined by the responsible clinician.

CMR protocol

Scans were performed in accordance with local protocol (including localizers, short-axis and long-axis cine imaging, perfusion imaging and late gadolinium enhancement imaging) using a 1.5T MR scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany). Patients were asked to refrain from caffeine for at least 12 hours prior to the scan. Basal, mid-ventricular and apical short-axis perfusion images were acquired both at rest and during adenosine hyperaemia. The perfusion sequence used has been described previously(8). In brief, the sequence utilised a dual sequence approach with separate pulse sequences for the arterial input function (AIF) and myocardial tissue. Image acquisition was performed over 60

heart beats with a bolus of 0.05mmol/kg gadoterate meglumine (Dotarem, Guerbet SA, Paris, France) administered at 4 ml/sec followed by a 20 ml saline flush during acquisition of each perfusion sequence. Each patient received a total of 0.10mmol/kg gadoterate meglumine. The arterial input function (AIF) was calculated using the left ventricular (LV) blood pool signal which was automatically segmented from optimised low-resolution images acquired in parallel with higher spatial resolution images used for estimating myocardial perfusion. Myocardial perfusion was calculated using a blood tissue exchange model(15) after corrections to minimise T2* losses and for non-linearity of saturation recovery, and pixel-wise perfusion maps were automatically generated in-line.

Hyperaemia was induced using adenosine infused via a peripheral cannula at a rate of 140mcg/kg/min for 4 minutes with a further 2 minutes at 175mcg/kg/min if there was evidence of insufficient stress such as no heart rate response and no symptoms.

CMR Image Analysis

Image analysis was performed offline using Osirix MD 9.0 (Bernex, Switzerland). First-pass images were analysed visually by an experienced observer blinded to the findings of the coronary angiogram and perfusion maps. Each myocardial segment (based on the 17-segment model excluding the apical cap) was assessed for the presence of a perfusion defect and each study graded for perfusion defects by coronary territory (defined as at least two adjacent segments within an AHA-defined coronary territory with visual perfusion detects). For patient-level analysis, a study was graded as positive if two adjacent segments displayed visual perfusion defects.

For quantitative analysis of perfusion maps, the endo- and epicardial borders were manually delineated for each basal, mid-ventricular and apical short-axis perfusion map. Obvious image artefacts and coronary arteries were excluded from the regions of interest.

Using a custom-made plug-in, the maps were split into 16 segments. A coronary territory was defined as ischaemic by perfusion mapping if two adjacent segments within an AHA-defined coronary territory each demonstrated stress MBF <1.94ml/g/min(9). For patient-level analysis, a study was graded as positive if two adjacent segments displayed average stress MBF <1.94ml/g/min.

When assessing methods for detection of no CAD, single-vessel or MVCAD, each coronary territory was defined as being ischaemic if >2 segments had average MBF <1.94ml/g/min for perfusion maps and >2 segments had visible defects for first-pass perfusion. The method was graded as correct if the ischaemic territories matched the coronary vessels with obstructive disease.

Myocardial ischaemic burden (IB) was assessed using perfusion maps (defined as percentage of myocardial segments with stress MBF <1.94ml/g/min) and using first-pass perfusion images (defined as percentage of myocardial segments with visual perfusion defect on first-pass perfusion images).

Statistical analysis

All continuous variables were tested for normal distribution (Shapiro-Wilk test). Normally distributed metrics are summarized by the mean ± standard deviation (SD). Mean values were compared using paired Student's T-test. Nominal data were compared using the χ^2 test. Paired proportions were compared using McNemar's exact test. Continuous variables across groups were compared using one-way analysis of variance (ANOVA) with post-hoc Bonferroni correction for normally distributed parameters and Kruskal-Wallis test for non-normally distributed parameters. Proportions across groups we compared using the χ^2 test. No corrections for multiple observations within individuals were made for segment-wise

analysis. Statistical analysis was performed using IBM SPSS Statistics Version 24 (IBM, Somers, New York).

RESULTS

A total of 151 patients (mean age 64±11 years, 73 (77%) male) were enrolled including 95 with MVCAD (47 with 3VD and 48 with 2VD), 31 with single-vessel disease and 25 with unobstructed coronaries. FFR was measured in 92 (20%) vessels, with FFR being negative in 62 (67%) of vessels. In total 61 (13%) vessels were chronic total occlusions, with all having angiographic evidence of collateral flow from another vessel. Figure 1 shows examples of perfusion maps of patients with 3VD, single-vessel disease and unobstructed coronaries.

Mean time between CMR and coronary angiography was 8±68 days and in 77% of cases the two tests were less than 2 months apart. Seventy patients (46%) had evidence of subendocardial or transmural late gadolinium enhancement in at least one myocardial segment. Patient demographics are summarized in Table 1. There were significantly more females in the unobstructed coronaries group and hypertension was more frequent in patients with MVCAD (table 2). A higher proportion of patients with MVCAD had previous myocardial infarction (defined by presence of subendocardial or transmural late gadolinium enhancement) or at least one chronic total occlusion.

Detection of obstructive coronary artery disease

At a patient-level, perfusion mapping was able to correctly differentiate obstructive CAD from non-obstructive CAD with sensitivity 84% (95% confidence interval (CI) 64-95%), specificity 95% (90-98%) and accuracy 93% (86-98%). VA was able to detect obstructive CAD with sensitivity 92% (74-99%) specificity 95% (90-98%) and accuracy 95%

(87-98%). Global stress MBF >2.20ml/g/min was able to detect obstructive CAD with sensitivity 79% (70-85%), specificity 100% (86-100%) and area-under the receiver-operator curve (AUC) 0.92 (0.86-0.96).

Detection of multivessel disease

In patients with MVCAD, perfusion mapping identified significantly more myocardial segments with perfusion defects compared to VA (median segments per patient 12 (interquartile range (IQR) 9-16) by perfusion mapping vs 8 (IQR 5-9.5) by VA, p<0.001) (Figure 2). In patients with single-vessel disease, there was no difference in number of ischaemic segments detected (4 (IQR 2-7) by perfusion mapping vs 4 (IQR 2-5) by VA, p=0.166). Overall, 270/453 (60%) coronary perfusion territories were defined as ischaemic using perfusion maps compared to 210/453 (46%) using visual analysis (p<0.001). An additional 34/453 (7.5%) perfusion territories had only one ischaemic segment by perfusion mapping (therefore graded as negative) and of these 24 (71%) were subtended by an artery with no obstructive lesion.

In those with 3VD, perfusion defects were identified in all three coronary territories in 41/47 (87%) cases using perfusion maps compared to 19/47 (40%) cases by VA (p<0.001). Using VA, 22/47 (47%) cases were misclassified as 2VD and 6/47 (13%) as single-vessel disease. Using perfusion mapping 6/47 (13%) cases were misclassified as 2VD and no cases classified as single-vessel disease or unobstructed coronaries (Figure 3).

2VD was correctly identified in 34/48 (71%) cases using perfusion mapping compared to 23/48 (48%) cases using VA (p=0.03). Single-vessel disease was correctly identified in 22/31 (71%) cases using both perfusion mapping and VA. Non-obstructive disease was correctly identified in 21/25 (84%) cases using perfusion mapping and 23/25 (92%) cases using VA (Figure 4).

The overall accuracy of perfusion mapping to correctly identify extent of coronary disease was 78% compared to 58% for VA ($p<0.001$)

Assessment of ischaemic burden

Using both perfusion mapping and VA of first-pass perfusion images, IB increased as number of vessels with obstructive disease increased (Figure 5). In patients with MVCAD, IB measured using perfusion mapping was significantly higher than IB measured using VA (3VD: maps 100% (IQR 75-100%) vs VA 56% (IQR 38-81%), $p<0.001$; 2VD: maps 63% (IQR 50-75%) vs VA 41% (IQR 31-50%), $p<0.001$). In patients with no obstructive CAD and single-vessel disease, there was no difference in IB measured by mapping or VA of first-pass perfusion (no CAD: maps 0% (IQR 0-6%) vs VA 0% (IQR 0-0%); single-vessel disease: maps 25% (IQR 13-44%) vs VA 25% (IQR 13-31%); p=NS for both).

DISCUSSION

This study demonstrates that quantitative myocardial perfusion mapping increases the accuracy of CMR in differentiating 3VD or 2VD from single-vessel CAD, doubling the number of correctly identified cases of 3VD compared to VA. Furthermore, in patients with MVCAD, IB measured using perfusion mapping is greater than that identified using traditional VA of first-pass perfusion imaging.

Identification of perfusion defects in multivessel disease

MVCAD is a common finding in patients with angina attending for coronary angiography and current guidelines recommend revascularization based upon demonstration of ischaemia either with invasive physiology or using non-invasive assessment(13). However, most studies of stress perfusion CMR to date have focused on the ability to detect

obstructive CAD at a patient level (i.e. positive or negative) rather than attempt to differentiate MVCAD from single-vessel disease(16,17). We have previously demonstrated that quantitative perfusion mapping is accurate for the detection of obstructive CAD at a coronary artery level(9). In this study, we provide additional data showing the technique can be used assess extent of CAD in a larger cohort enabling identification of patients with more extensive CAD.

Our data suggest that less than half of cases are correctly graded as 2VD or 3VD when first-pass images are analyzed visually. This is consistent with data from Motwani M et al(5) who found that only 29% of patients with 3VD had perfusion defects in all 3 coronary territories with standard resolution perfusion CMR although this improved to 57% with high resolution imaging. The only other study assessing the same question found perfusion defects in all three territories in 58% of cases with 3VD(7). In the present study, perfusion mapping correctly identified 3VD in 87% of cases and 2VD in 71% cases. We propose that this difference is due to the fact that, when analyzing images visually, the eye is drawn to the most prominent defects (Figure 2), which should be associated with the coronary artery with the most severe stenosis or in regions with prior myocardial infarction. Other territories may also have reduced perfusion but may appear "normal" compared to a severe perfusion defect when visualizing greyscale images. Using color-coded pixelwise maps, areas of reduced perfusion can be easily recognized visually and, more importantly, be measured quantitatively. Furthermore, these results outperform previously published studies of CMR perfusion in multivessel disease(5,7).

The threshold used to define a coronary perfusion territory as ischaemic in this study was 2 adjacent segments using the AHA-defined coronary territory model. This is consistent with the method used in the CE-MARC2 study(18), but others have previously used one myocardial segment(17,19). Within our cohort, 7.5% of coronary perfusion territories had

only one ischaemic segment (therefore graded as negative) but of these less than one-third were subtended by coronary arteries with an obstructive stenosis. Our data suggests that a 2 adjacent segment model to define ischaemia provides good sensitivity and specificity for identification of ischaemia.

Stress perfusion CMR is increasingly being requested as a clinical test in patients with known CAD for the assessment of regional ischaemia and ischaemic burden in order to guide revascularization strategies. In this situation, it is imperative to correctly identify all areas of ischaemia as this may be the difference between coronary artery bypass surgery (CABG) and PCI particularly in the setting of 3VD, or between PCI and medical therapy for a given stenosis. Our data suggest that by significantly increasing the diagnostic accuracy in the identification of MVCAD CMR perfusion mapping could potentially lead to improvement in patient management.

Evaluation of ischaemic burden

It has been shown using PET that extent of cardiac ischaemia is a marker of patient prognosis and that revascularization confers a survival benefit in those with high ischaemic burden(20,21). Data using CMR are limited, with studies to date measuring ischaemic burden based on proportion of segments with perfusion defects(5,22). It has been suggested that PET derived-thresholds of >10% ischaemic burden being significant can be translated to CMR however evidence for this is limited(23-25). Recently, Sammut EC et al showed that ischaemic burden >10% measured by semi-quantitative CMR methods was predictive of adverse prognosis. The results of the present study demonstrate that myocardial perfusion maps more accurately detect areas of ischaemia, as defined by invasive coronary physiology, compared to visual first pass perfusion. As expected, ischaemic burden increases with number of coronary arteries affected and this is consistent with data from Patel AR et al who

demonstrated an ischaemic burden of 60% in patients with three-vessel disease compared to 25% in those with single vessel disease(6). Within our cohort, patients with 3VD had an median ischaemic burden of 56% (IQR 38-81%) using VA of first-pass perfusion and 100% (IQR 75-100%) using perfusion mapping whereas those with single-vessel disease had comparable ischaemic burden using the two methods (median 25% (IQR 13-31%) using VA of first-pass vs 25% (IQR 13-44%) using mapping). This is consistent with our hypothesis that visual analysis underestimates ischaemic burden in more extensive coronary disease. Perfusion mapping also opens up the possibility of analysis if ischaemic burden at a pixel-level rather than averaging across myocardial segments. However, this method is limited by factors such as microvascular dysfunction, normal variability in blood flow and false positive areas of reduction in MBF, which may result in pixels of blood flow reduction in areas of normal myocardium.

Translation to clinical practice

The quantitative perfusion mapping sequence used in this study is simple to acquire using a dual-sequence approach (requiring a single injection of contrast for each acquisition rather than the two boluses required for many other quantitative perfusion sequences) with perfusion maps being reconstructed automatically and displayed inline on the scanner within minutes. The pixel-wise maps are generated in addition to traditional first-pass perfusion images allowing the user to review both. Quantitative analysis is simple to perform and full automatization of myocardial contouring and generation of MBF values has recently been developed(26). This approach can therefore be readily translated to clinical practice providing information additional to the first-pass images and which may assist in clinical decision making both for correct diagnosis of severity of CAD and also to guide revascularization strategies.

Limitations

This is a relatively small sample size where both coronary angiography and stress CMR were requested for clinical reasons and therefore there is likely to have been patient selection bias. There was a high proportion of patients with obstructive disease as in clinical practice the majority of patients with normal CMR perfusion would not proceed to invasive coronary angiography. However, as the aim of this study was to investigate the extent of coronary disease rather the presence or absence, the results are still relevant to clinical practice. Thirty patients within this cohort were also included in a previously published study(9) but the analysis performed in this study was different to that performed in the previous study. The time window between CMR and angiography was within 6 months in order to maximize the inclusion of suitable cases. Whilst severity of coronary disease may worsen over time, we do not expect this to be the relevant in this cohort as the time between tests was short for the majority of patients.

The dose of gadolinium contrast used in this study was 0.05mmol/kg for each perfusion sequence acquired as it is known that the relationship between gadolinium concentration and signal intensity becomes non-linear at higher gadolinium doses. Whilst the relatively low dose may have contributed to lower sensitivity of visual analysis it is the same dose as that used in a number of other studies of stress perfusion CMR(16,18,27).

The reference standard used in this study was a combination of FFR and visual analysis of angiographic images. It would have been preferable to measure FFR in all epicardial vessels, but this was not possible due to the logistics of performing multiple FFR measurements in patients with severe and often complex multivessel coronary disease. However, FFR was measured in all vessels with intermediate grade stenoses and in the absence of chronic total occlusions.

Overall, the findings support added benefit of quantitative perfusion maps at a technical level but further larger studies with clinical outcome data would be required to support its routine use for risk stratification.

Conclusions

Visual analysis of first-pass stress perfusion underestimates ischaemic burden compared to pixelwise quantitative myocardial perfusion mapping, which significantly increases the accuracy of CMR in assessment of ischemic burden and in differentiating 3VD and 2VD from single-vessel CAD. This has important implications for assessment of ischaemia and therapeutic decision making.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge: Stress perfusion CMR is a validated tool for the assessment of coronary artery disease. However, visual analysis of first-pass perfusion may underestimate the extent of ischaemia in multivessel disease

Translational Outlook: This study demonstrates that identification of multivessel disease is improved by using quantitative CMR perfusion mapping. A larger study with clinical endpoints would be useful to justify the routine use of perfusion mapping for the assessment and risk stratification of patients with coronary artery disease.

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FIGURES

Figure 1: Stress myocardial perfusion maps.
Examples of stress myocardial perfusion maps, first pass perfusion images and coronary angiograms of a patient with unobstructed coronaries, single-vessel disease and three-vessel disease. Arrows point to areas of significant stenosis. Patient with single vessel disease has a critical stenosis in the mid left anterior descending artery (black arrow) and unobstructed circumflex (FFR 0.94) and right coronary artery (FFR 0.98). Patient with three-vessel disease has severe proximal obstructive disease in all three vessels (black arrows).

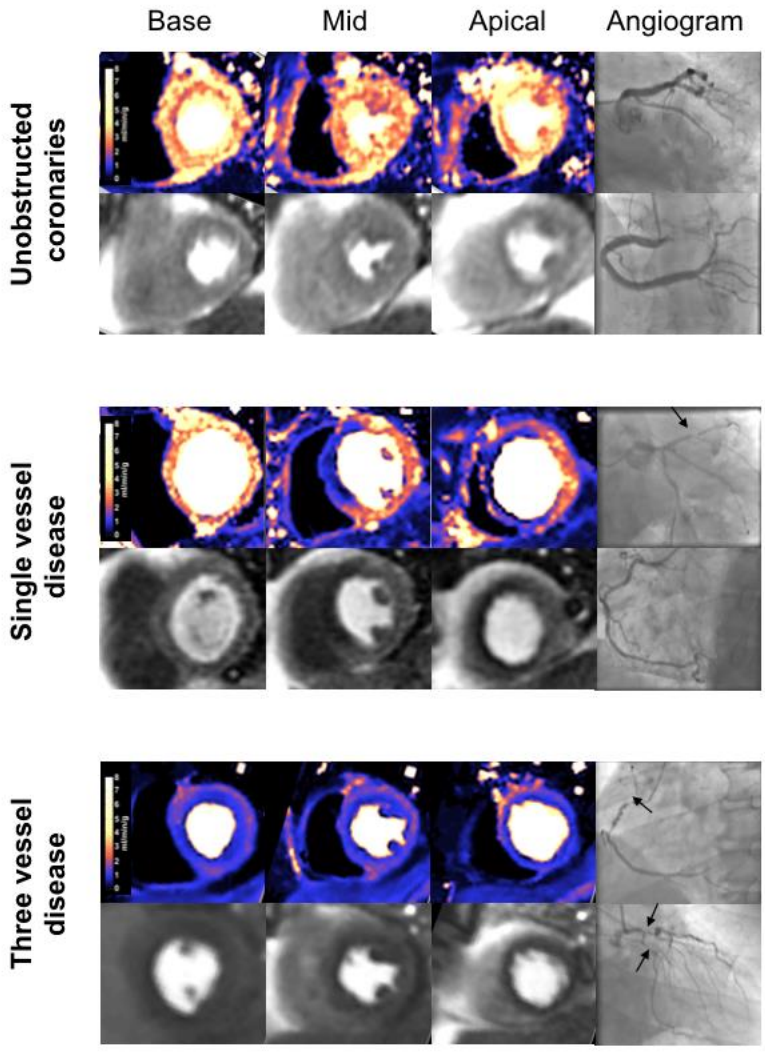


Figure 2: Underestimation of ischaemia by first-pass perfusion.
Examples of first pass perfusion images, myocardial perfusion maps and coronary angiography of two patients with obstructive three-vessel disease. In example 1, visual analysis demonstrates discrete areas of perfusion defects whereas perfusion maps show more extensive global ischaemia. In example 2, visual analysis shows a prominent perfusion defect in the inferior wall whereas perfusion maps show diffuse reduction in blood flow and consistent with coronary angiogram showing severe three vessel disease. Myocardial blood flow values for each segment are in ml/g/min.

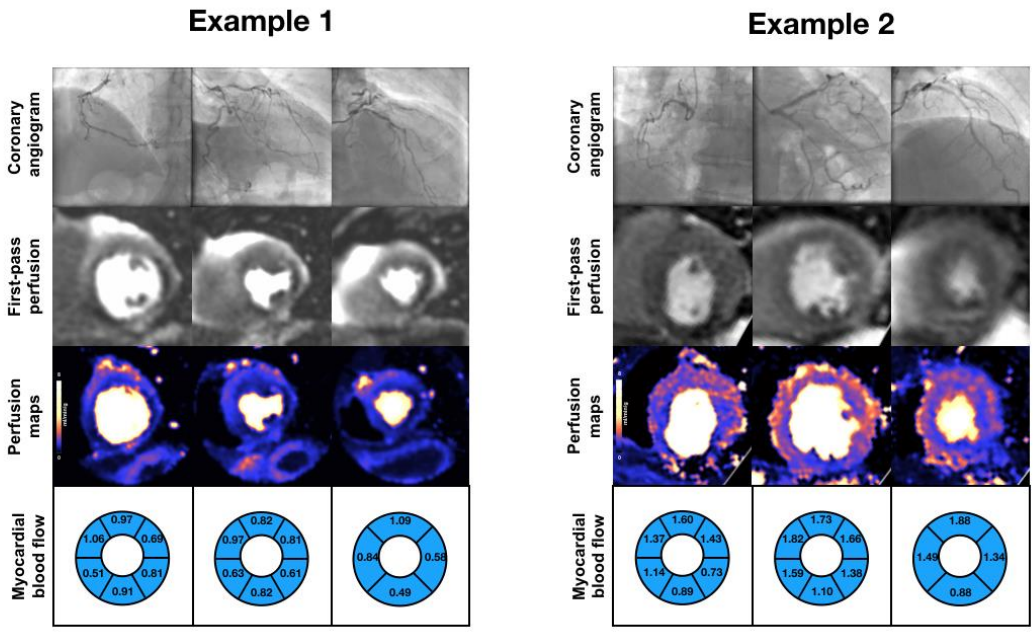


Figure 3: Grading of extent of coronary disease in patients with confirmed obstructive three-vessel disease using perfusion maps and by visual analysis.
Use of myocardial perfusion maps results in more patients being correctly identified as three-vessel disease compared to by visual analysis of first pass perfusion images (values within chart represent number of cases).

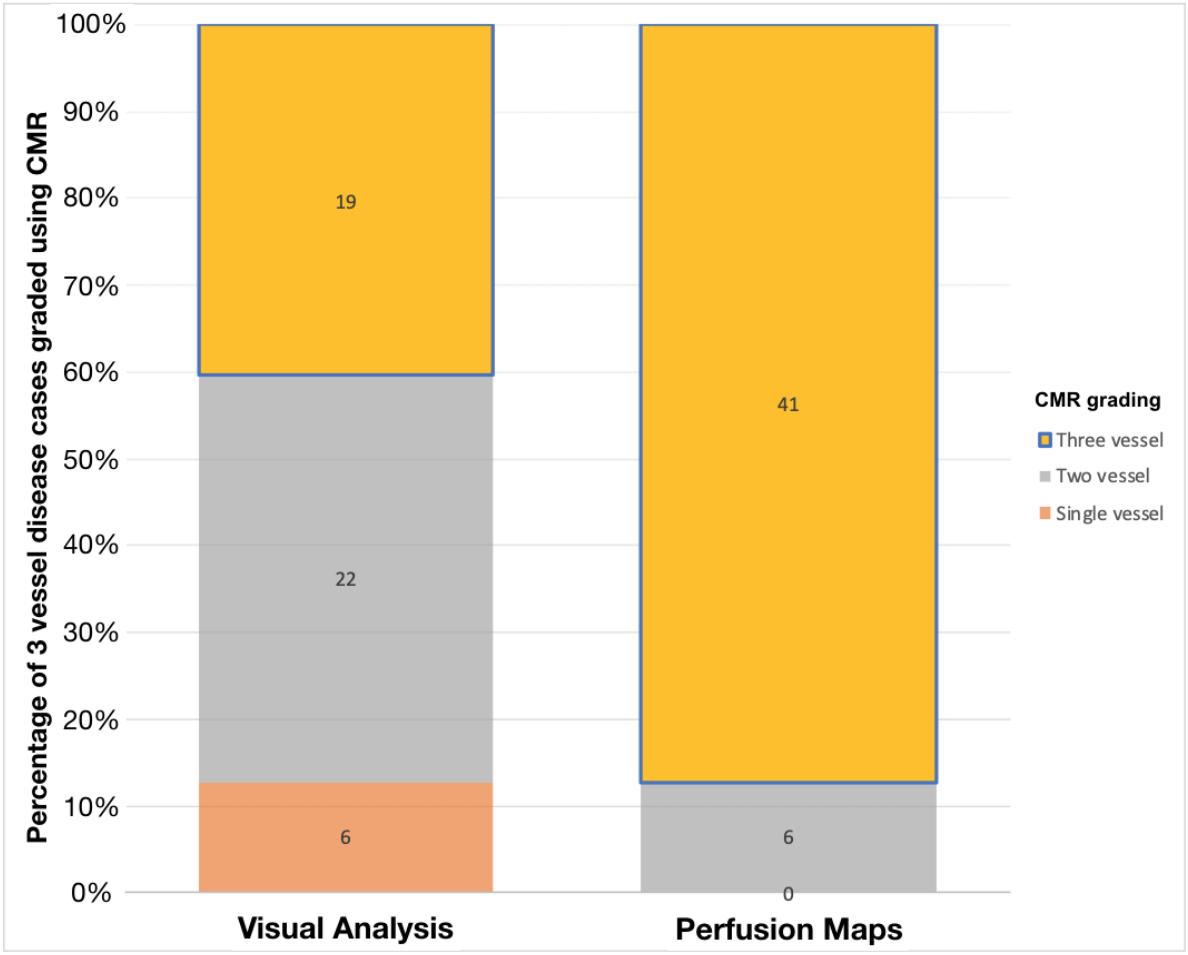


Figure 4: Percentage of cases correctly classified by perfusion mapping and visual analysis of first pass perfusion.
A significantly higher proportion of two-vessel and three-vessel cases are correctly identified compared to visual analysis with no significant difference for single-vessel disease and unobstructed coronaries

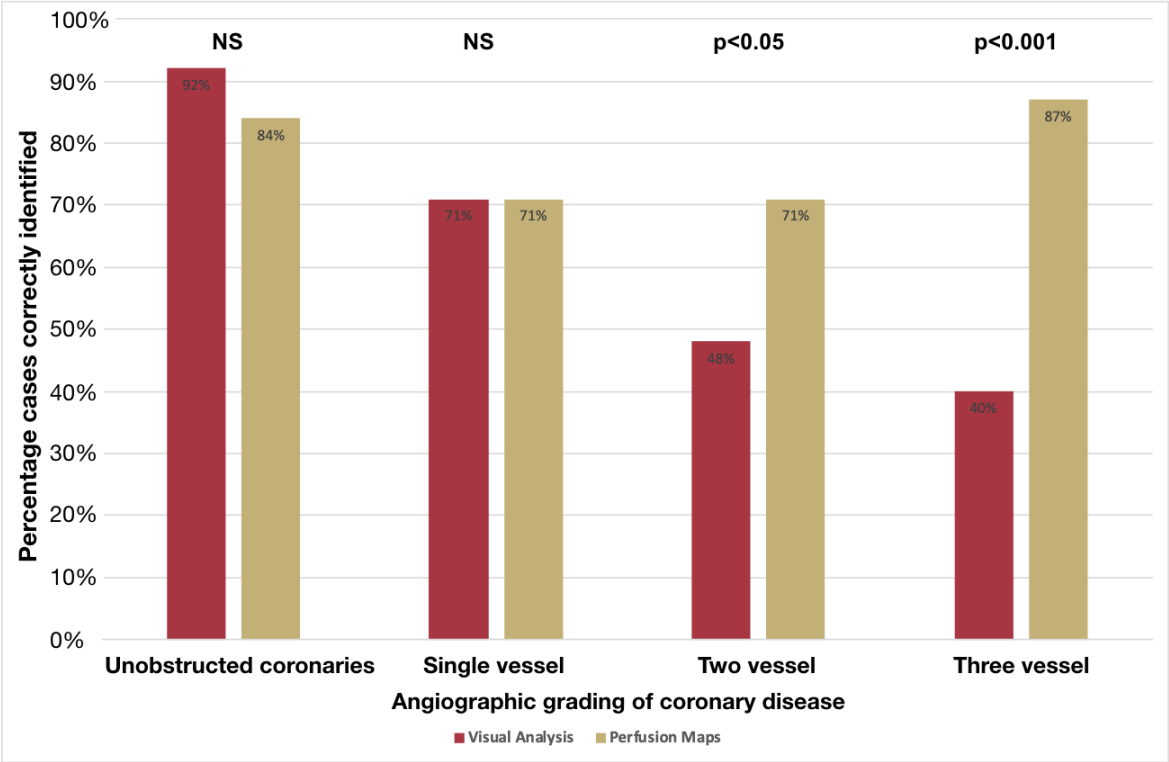
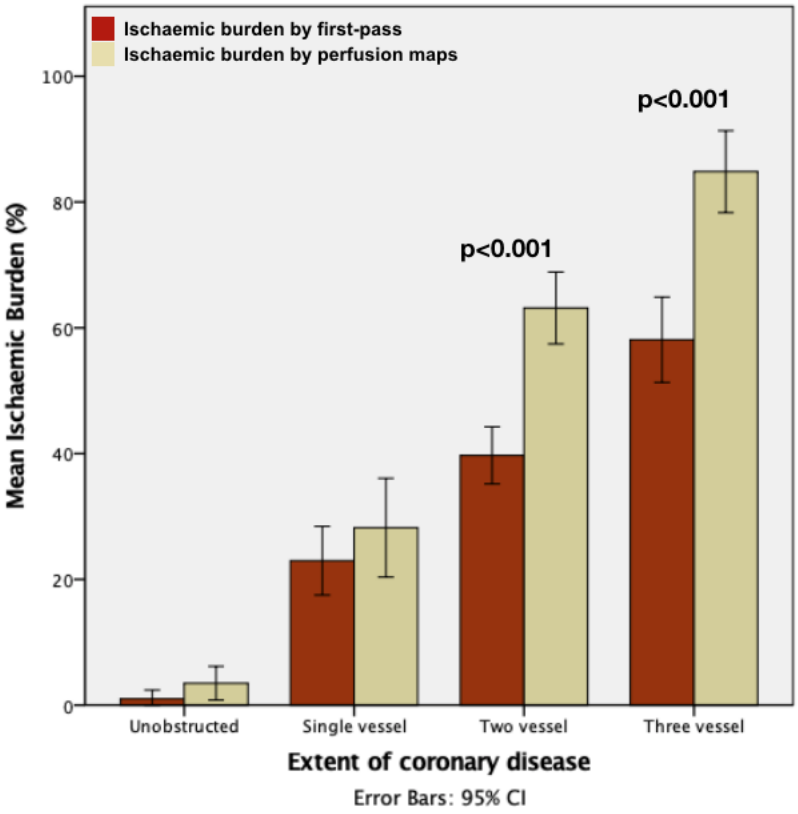
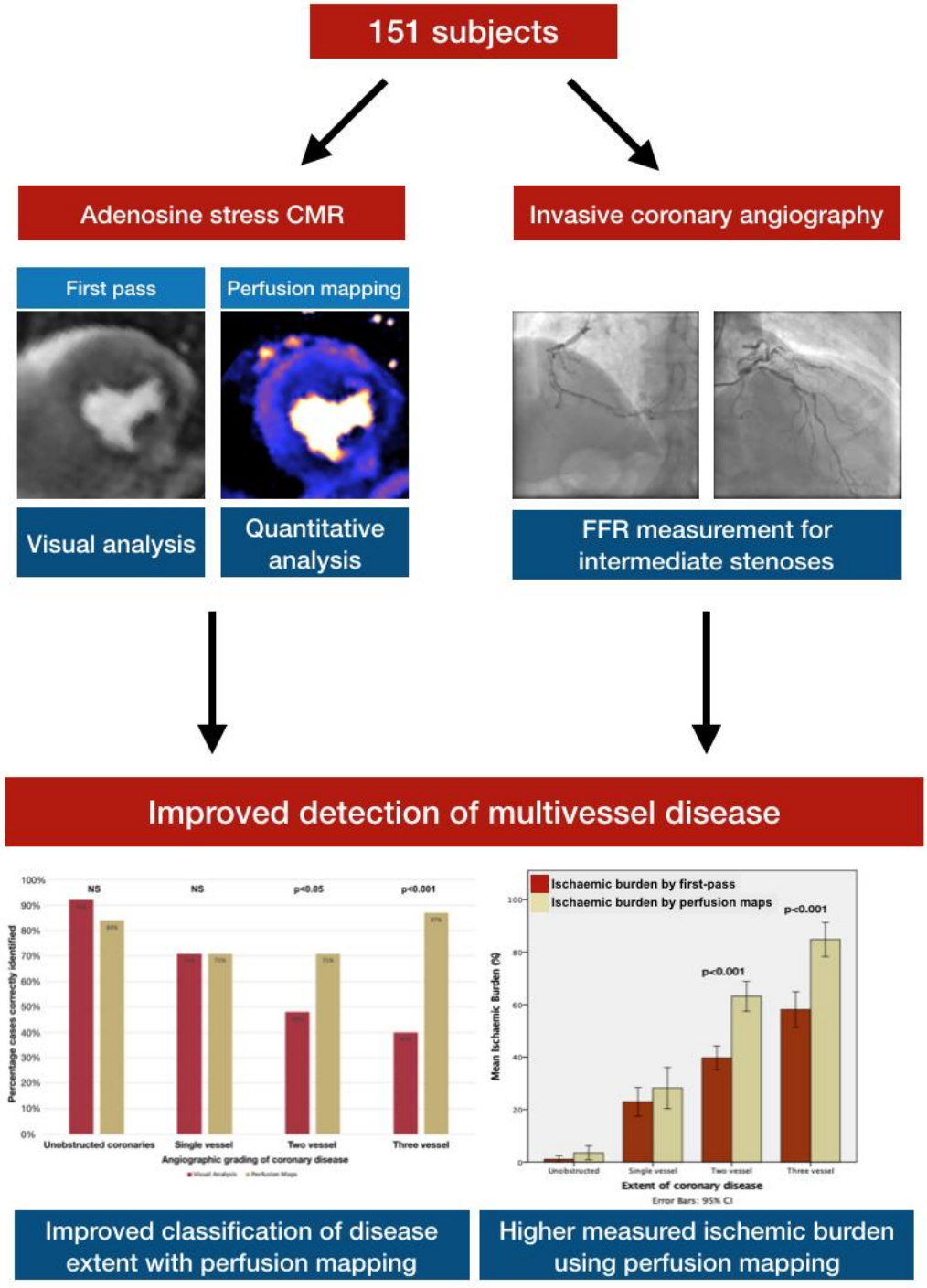


Figure 5: Ischaemic burden in coronary artery disease.
Ischaemic burden (IB) measured using first-pass perfusion and perfusion maps with increasing severity of coronary artery disease



Central Illustration: Perfusion mapping in multi vessel disease.
A significantly higher proportion of two-vessel and three-vessel cases are correctly identified compared to visual analysis with no significant difference for single-vessel disease and unobstructed coronaries


151 subjects
Adenosine stress CMR
Invasive coronary angiography
First pass
Perfusion mapping
Visual analysis
Quantitative analysis
FFR measurement for intermediate stenoses
Improved detection of multivessel disease
Percentage cases correctly identified
NS
NS
p<0.05
p<0.001
Unobstructed coronaries
Single vessel
Two vessel
Three vessel
Angiographic grading of coronary disease
Ischaemic burden by first-pass
Ischaemic burden by perfusion maps
p<0.001
p<0.001
Mean Ischaemic Burden (%)
Extent of coronary disease
Error Bars: 95% CI
Improved classification of disease extent with perfusion mapping
Higher measured ischemic burden using perfusion mapping

Tables

Table 1: Baseline clinical characteristic

Age, years	64±11
Males	120 (80%)
Medical History	
Hypertension	99 (66)
Diabetes Mellitus	56 (37)
Hyperlipidaemia	112 (74)
Current smoker	25 (17)
Ex-smoker	48 (32)
Previous PCI	61 (40)
Angiography findings	
No significant disease	25 (17)
One-vessel disease	31 (21)
Two-vessel disease	48 (32)
Three-vessel disease	47 (31)
LAD disease	102 (68)
Cx disease	72 (48)
RCA disease	93 (62)

Values shown are numbers in each group with percentages in brackets.

Cx: circumflex artery; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery.

Table 2: Comparison of demographics and risk factors between groups with increasing severity of coronary disease

	No obstructive disease (n=25)	One-vessel disease (n=31)	Two-vessel disease (n=48)	Three-vessel disease (n=47)	P-value
Age, years	64±9	63±12	65±11	66±12	0.756
Males	11 (44%)	28 (90%)	40 (83%)	41 (87%)	**<0.001**
Hypertension	14 (56%)	14(45%)	35 (73%)	36 (77%)	**0.009**
Diabetes mellitus	7 (28%)	7 (23%)	24 (50%)	18 (38%)	0.123
Hyperlipidaemia	14 (56%)	25 (81%)	35 (73%)	38 (81%)	0.074
Previous PCI	4 (16%)	5 (16%)	13 (27%)	12 (26%)	0.222
Previous MI*	0 (0%)	9 (29%)	31 (65%)	30 (64%)	**<0.001**
At least one CTO vessel	0 (0%)	7 (23%)	23 (48%)	23 (49%)	**<0.001**

Age represented as mean ± standard deviation. All others are number in each category with percentages in brackets.

*previous MI defined as subendocardial or transmural late gadolinium enhancement in at least one myocardial segment

CTO: chronic total occlusion; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 3: Comparison of ischaemic burden measured by visual analysis and perfusion maps between groups with increasing severity of coronary disease

	No obstructive disease	One-vessel disease	Two-vessel disease	Three-vessel disease	p-value
Segments with perfusion defects by visual analysis	0 (0-0)	4 (2-5)	6.5 (5-8)	9 (6-13)	<**0.001**
Segments with perfusion defects by perfusion maps	0 (0-1)	4.0 (2-7)	10 (8-12)	16 (12-16)	<**0.001**
Global average stress MBF, ml/g/min	2.83±0.54	2.29±0.49	1.76±0.44	1.32±0.47	<**0.001**
Ischaemic burden by first-pass perfusion, %	0 (0-0)	25 (13-31)	41 (31-50)	56 (38-81)	<**0.001**
Ischaemic burden by perfusion maps, %	0 (0-6)	25 (13-44)	63 (50-75)	100 (75-100)	<**0.001**

MBF: myocardial blood flow. Global average stress MBF is represented as mean ± standard deviation. All other parameters are represented as median (1^{st} quartile – 3^{rd} quartile).

Video Legends:

Video 1. Figure 1 unobstructed coronaries
First pass perfusion video of unobstructed coronaries case from Figure 1

Video 2. Figure 1 single vessel disease
First pass perfusion video of single vessel disease case from Figure 1

Video 3. Figure 1 three vessel disease
First pass perfusion video of three vessel disease case from Figure 1

Video 4. Figure 2 example 1
First pass perfusion video of example 1 from Figure 2

Video 5. Figure 2 example 2
First pass perfusion video of example 2 from Figure 2