

The Prognostic Significance of Quantitative Myocardial Perfusion: An Artificial Intelligence Based Approach Using Perfusion Mapping

Running Title: *Knott et al.; The Prognostic Utility of AI Perfusion Mapping*

Kristopher D. Knott, MBBS^{1,2}; Andreas Seraphim, MBBS^{1,2}; Joao B. Augusto, MD^{1,2};
Hui Xue, PhD³; Liza Chacko, MBBS^{1,4}; Nay Aung, MBBS^{2,5}; Steffen E. Petersen, DPhil^{2,5};
Jackie A. Cooper, MSc⁵; Charlotte Manisty, PhD^{1,2}; Anish N. Bhuvu, MBBS^{1,2};
Tushar Kotecha, MBChB^{1,4}; Christos V. Bourantas, PhD^{1,2}; Rhodri H. Davies, PhD^{1,2};
Louise A.E. Brown, MBChB⁶; Sven Plein, MD PhD⁶; Marianna Fontana, PhD^{1,4};
Peter Kellman, PhD³; James C. Moon, MD^{1,2}



¹Institute of Cardiovascular Science, University College London, London, UK; ²Barts Heart Centre, St Bartholomew's Hospital, London, UK; ³National Heart, Lung, and Blood Institute, National Institutes of Health, DHHS, Bethesda, MD; ⁴Royal Free Hospital, London, UK; ⁵William Harvey Research Institute, Queen Mary University of London, UK; ⁶Department of Biomedical Imaging Science, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Clarendon Way, Leeds, UK

Address for Correspondence:

James C. Moon, MD
Barts Heart Centre
West Smithfield
London, UK, EC1A 7BE
Tel: +44 2039316477
Email: j.moon@ucl.ac.uk

Abstract

Background: Myocardial perfusion reflects the macro- and microvascular coronary circulation. Recent quantitation developments using cardiovascular magnetic resonance (CMR) perfusion permit automated measurement clinically. We explored the prognostic significance of stress myocardial blood flow (MBF) and myocardial perfusion reserve (MPR, the ratio of stress to rest MBF).

Methods: A two center study of patients with both suspected and known coronary artery disease referred clinically for perfusion assessment. Image analysis was performed automatically using a novel artificial intelligence approach deriving global and regional stress and rest MBF and MPR. Cox proportional hazard models adjusting for co-morbidities and CMR parameters sought associations of stress MBF and MPR with death and major adverse cardiovascular events (MACE), including myocardial infarction, stroke, heart failure hospitalization, late (>90 day) revascularization and death.

Results: 1049 patients were included with median follow-up 605 (interquartile range 464-814) days. There were 42 (4.0%) deaths and 188 MACE in 174 (16.6%) patients. Stress MBF and MPR were independently associated with both death and MACE. For each 1ml/g/min decrease in stress MBF the adjusted hazard ratio (HR) for death and MACE were 1.93 (95% CI 1.08-3.48, P=0.028) and 2.14 (95% CI 1.58-2.90, P<0.0001) respectively, even after adjusting for age and co-morbidity. For each 1 unit decrease in MPR the adjusted HR for death and MACE were 2.45 (95% CI 1.42-4.24, P=0.001) and 1.74 (95% CI 1.36-2.22, P<0.0001) respectively. In patients without regional perfusion defects on clinical read and no known macrovascular coronary artery disease (n=783), MPR remained independently associated with death and MACE, with stress MBF remaining associated with MACE only.

Conclusions: In patients with known or suspected coronary artery disease, reduced MBF and MPR measured automatically inline using artificial intelligence quantification of CMR perfusion mapping provides a strong, independent predictor of adverse cardiovascular outcomes.

Key Words: myocardial perfusion; cardiovascular outcomes; inline perfusion quantification; cardiovascular magnetic resonance.

Nonstandard Abbreviations and Acronyms

AF	Atrial Fibrillation
AI	Artificial Intelligence
AIF	Arterial Input Function
BHC	Barts Heart Centre
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCS	Chronic Coronary Syndromes
CNN	Convolution Neural Net
CFR	Coronary Flow Reserve
CMR	Cardiovascular Magnetic Resonance
EDV	End Diastolic Volume
EF	Ejection Fraction
FFR	Fractional Flow Reserve
HR	Hazard Ratio

HRA	Health Research Authority
IMR	Index of Microcirculatory Resistance
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
MACE	Major Adverse Cardiovascular Events
MBF	Myocardial Blood Flow
MI	Myocardial Infarction
MICE	Multiple Imputation by Chained Equations
MPR	Myocardial Perfusion Reserve
NHS REC	National Health Service Research Ethics Committee
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
RFH	Royal Free Hospital
SPECT	Single Photo Emission Tomography
T	Tesla
TIA	Transient Ischemic Attack



Circulation

Clinical Perspective

What is new?

- Perfusion mapping uses artificial intelligence to provide instantaneous quantification of myocardial perfusion by CMR.
- Quantitative myocardial blood flow provides incremental prognostic information in patients with suspected coronary artery disease above traditional cardiovascular risk factors.
- Even in patients without regional perfusion defects, absolute perfusion is prognostic.

What are the clinical implications?

- Absolute perfusion quantification is a likely new biomarker in patient care.
- As there is no user input and no ionising radiation, early disease and microvascular disease can be studied at scale
- Impaired global perfusion may be a targetable cardiovascular risk factor.



Circulation

Introduction

Cardiovascular disease is the leading global cause of mortality and morbidity (1) with chronic coronary syndromes (CCS) a leading contributor. CCS include macrovascular epicardial coronary artery (CAD) and microvascular dysfunction (2), both resulting in reduced myocardial blood flow and adverse outcomes (3), but are amenable to medical and interventional therapies (4). Invasive assessment strategies (fractional flow reserve, FFR, and the index of microcirculatory resistance, IMR) (5,6) to measure blood flow are now recommended by international guidelines but these are associated with risk (7,8). Non-invasive, functional perfusion testing has not superseded this strategy because it has not yet demonstrated sufficient prognostic importance and is frequently assessed qualitatively.

Functional perfusion tests include Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) and Cardiovascular Magnetic Resonance (CMR). All are accurate for the detection of epicardial CAD (9), but by measuring tissue blood flow, they additionally capture microvascular disease which is an advantage for understanding the whole myocardial circulation. Using PET, absolute quantification of myocardial blood flow (MBF) and the ratio of stress to rest MBF, known as the myocardial perfusion reserve (MPR) or coronary flow reserve (CFR) can be performed. Quantitative PET perfusion encodes prognostic information in suspected CCS (10–13) and cardiomyopathy (14) and is potentially less operator dependent and less likely to miss balanced ischemia than qualitative techniques.

An alternative to PET that does not use ionizing radiation is CMR. Stress perfusion CMR has been validated against intracoronary blood flow for detecting CAD (15,16) with death and major adverse cardiovascular events (MACE) at one year being similar between patients managed initially with stress perfusion CMR or FFR guided strategies (17). Unlike PET

perfusion, CMR has been primarily qualitative to date due to the complexity and time needed for quantitation. This is now changing with the development of new quantitative techniques.

“Perfusion Mapping” is an approach where, in addition to conventional images, perfusion maps are generated automatically on the scanner with each image pixel encoding MBF (ml/g/min) (18). The technique has been validated in healthy volunteers, against PET, coronary angiography and invasive physiology and provides insight into microvascular function in cardiomyopathy (19–23). Latest software iterations using artificial intelligence approaches deliver automatic segmental and global quantitation, permitting efficient large-scale analysis. These artificial intelligence approaches have been applied to volume analysis in CMR and have the potential to provide precise, rapid image biomarkers of cardiac structure and function (24), but has not been applied to perfusion imaging before.



We sought to investigate whether, in a multicentre setting including all-comers, quantitative myocardial perfusion (global mean stress MBF and MPR) by CMR perfusion mapping would be independently associated with adverse outcomes.

Methods

All included data for this study are available from the corresponding author at reasonable request.

Patients

The study was approved by the National Health Service Research Ethics Committee (NHS REC) and Health Research Authority (HRA) and conducted in accordance with the Declaration of Helsinki (Barts Bioresource - REC ID 14/EE/0007, Royal Free Hospital – REC ID 07/H0715/101). We included consecutive patients aged 18 years and over referred to two centers

(Barts Heart Centre and the Royal Free Hospital, London UK), between March 2016 and August 2018 for stress perfusion CMR and who had provided written, informed consent and had >1 year follow-up available. We excluded patients diagnosed with inherited or infiltrative cardiomyopathies known to impact myocardial perfusion (such as hypertrophic cardiomyopathy and cardiac amyloid) from the analysis.

Patient co-morbidities and outcomes were documented from the electronic patient record and the NHS spine. Co-morbidities recorded were previous revascularization (PCI or CABG), CAD, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation (AF), stroke or transient ischemic attack (TIA), smoking and cancer. The study outcomes were all cause mortality and a composite of major adverse cardiovascular event (defined as myocardial infarction, stroke, heart failure admission, revascularization or death). Revascularization events <90 days after CMR were excluded to prevent the inclusion of events occurring as a result of the perfusion CMR. MACE was adjudicated by a committee of three cardiologists blinded to the perfusion data.

Cardiovascular Magnetic Resonance Scan

All scans were performed at 1.5 (Aera) or 3 Tesla (Prisma, Siemens Healthcare, Erlangen, Germany) according to a standard protocol including cine imaging, adenosine stress and rest perfusion and late gadolinium enhancement (LGE). Patients were asked to abstain from caffeine for 24 hours before the scan. All patients underwent adenosine stress according to a standard clinical protocol (25). Adenosine was infused at 140mcg/kg/min for four minutes. If there were no symptoms and no ≥ 10 beat per minute heart rate increase, the infusion rate was increased to 175mcg/kg/min (26,27). At maximal hyperemia, a gadolinium-based contrast agent (gadoterate meglumine, Dotarem, Guerbet, Paris, France) was injected at 4ml/s at a dose of 0.05mmol/kg.

Perfusion maps were generated automatically inline at the time of the scan according to (18). The acquisition was repeated at rest 5-10 minutes later (after the short axis stack).

Image analysis

All CMRs were analysed by a European Association of Cardiovascular Imaging or Society of Cardiovascular Magnetic Resonance (level 3) accredited cardiologist. Image analysis was performed using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). LV systolic, diastolic volume, ejection fraction, and the presence and distribution (infarct, or non-infarct) of late gadolinium enhancement were recorded.

Perfusion maps (3 short axis slices per patient) were generated automatically and inline at the time of the scan as described by Kellman et al 2017 (18). The perfusion sequence is a “dual sequence” technique (28) whereby there is a low-resolution arterial input function (AIF) acquisition and a high resolution myocardial perfusion acquisition simultaneously. Dual sequence perfusion quantification has been validated against microspheres (29). Perfusion is quantified for each pixel of myocardium (18) and perfusion maps are generated within 90s of the scan. Each pixel encodes the myocardial blood flow (ml/g/min). The AI tool performs automatic segmentation of the LV cavity and myocardium. It uses a convolution neural net (CNN) approach to delineate the LV cavity and myocardium, excluding myocardial fat and papillary muscles (30). The global MBF is then calculated automatically as an average of all pixels and global MPR as the ratio of stress to rest MBF. As they were contoured without user input, the perfusion data was blinded to other CMR and demographic parameters (Figure 1). Contoured perfusion maps were subsequently visually inspected by an observer (blinded to other parameters and outcome data) for quality control and discarded if there were errors. Following automatic AI

contouring, no human modification of contours was performed on any of the perfusion maps. The global mean stress MBF, rest MBF and MPR was recorded.

Statistical analysis

Statistical analysis was performed in SPSS (IBM SPSS statistics, Version 25.0). Continuous variables are presented as mean +/- standard deviation or median +/- interquartile range for normal and non-normally distributed data respectively. Categorical variables are presented as absolute values and percentages. Means were compared using the student T-test or Mann Whitney U test (depending on normality) for continuous variables and chi-square test (2-sided Fisher exact test) for categorical variables. A p value of <0.05 was considered statistically significant.

Cox proportional hazard regression analysis was performed to determine whether perfusion data (stress MBF and MPR) were associated with death and MACE adjusting for age, sex, co-morbidities (previous revascularization, CAD, hypertension, dyslipidemia, diabetes mellitus, AF, stroke / TIA, smoking and cancer) and CMR parameters (EDV, LVEF, LGE). A sensitivity analysis using a penalized model was performed to obtain Firth's bias-adjusted estimates to ensure there was no bias in the estimated coefficients due to low event rates (31). Kaplan Meier survival estimates were then plotted for the upper and lower 50th percentiles of stress MBF and MPR. Harrel's C-indices were used to compare the relative predictive ability of stress MBF and MPR. For this analysis, the data was censored at the date of death, MACE or last follow up.

The proportionality assumption was tested using the Schoenfeld residuals. The assumption was tested for each individual variable using a Bonferroni corrected significance level of $p < 0.0008$. Functional form was assessed by plotting deviance residuals against each

predictor variable and assessing the LOESS curve. Models were run with and without imputation of missing data. Both analyses gave similar results and only complete case results are shown. Multiple imputation by chained equations (MICE) was used to impute 10 complete datasets and results were pooled. Predictive mean matching with five nearest neighbours was used for continuous variables and logistic regression for binary variables. All variables used in the analysis models were included in the imputation.

Results

Patient demographics, comorbidities and CMR parameters

1356 eligible patients were referred for stress perfusion CMR, at Barts Heart Centre (BHC) and the Royal Free Hospital (RFH) between September 2016 and August 2018. Of these, 143 patients met the exclusion criteria and in 45 (3%) patients there was no apparent stress response via HR, symptoms, splenic switch off or myocardial vasodilatation, so we excluded these. 15 (1%) had perfusion map errors preventing analysis. 104 (8%) patients were lost to follow up. In total 1049 patients were included (889 BHC, 160 from RFH, Figure 2). In 31 patients, rest perfusion was not performed so there were 1018 patients who had MPR data.

The mean age was 60.9 +/-13 years, 702 (67%) were male, 298 (28%) had diabetes mellitus, 630 (60%) hypertension, 510 (49%) dyslipidemia, 318 (30%) previous revascularization, 360 (34%) smoking history, 63 (6%) previous stroke or TIA, 141 (13%) AF, 108 (10%) current or previous history of cancer. The mean EF 60% +/- 13%, 309 (30%) patients had infarct pattern and 133 (13%) non-infarct pattern LGE. Patient characteristics and CMR findings are summarized in Table 1. Mean stress MBF was 2.06+/-0.71 ml/g/min and mean MPR was 2.48+/-0.82.

Predictors of MACE

There were 42 (4.0%) deaths during a median following up period of 605 (interquartile range 464-814) days. In total there were 188 MACE in 174 (16.6%) patients. This included 28 (2.7%) myocardial infarctions, 10 (0.95%) strokes, 18 (1.7%) heart failure admissions and 127 (12.1%) late revascularizations. MBF was lower in those that died (1.70 ± 0.65 vs 2.08 ± 0.71 ml/g/min, $P=0.001$), as was MPR (1.97 ± 0.74 vs 2.50 ± 0.81 , $P<0.001$). Similar reductions occurred for total events (death or MACE) for both MBF and MPR, (both p values <0.001).

Patients that had a MACE were more commonly male, older, had more often prior revascularizations and were more likely to have diabetes, hypertension, dyslipidemia, a previous stroke or TIA and a positive smoking history. In addition, they had a lower LVEF and more often infarct pattern LGE (Table 2). For a breakdown of perfusion data and MACE for each site and field strength see Supplemental Table 1 and 2.

Cox hazard regression analysis demonstrated that stress MBF and MPR were associated with events after adjusting for potential confounders. The adjusted hazard ratio (HR) for 1 ml/g/min decrease in stress MBF was 1.93 (95% CI 1.08-3.48) for death ($P=0.028$) and 2.14 for MACE (95% CI 1.58-2.90, $P<0.0001$). The adjusted HR for a 1 unit decrease in MPR was 2.45 (95% CI 1.42-4.24) for death ($P=0.001$) and 1.74 (95% CI 1.36-2.22) for MACE ($P<0.0001$, Table 3). A standardized hazard model found the effect of MPR to be larger than stress MBF for death (standardized HR for a 1 SD reduction in MPR or MBF, 2.08 vs 1.56 respectively) but not for death or MACE (standardized HR 1.59 vs 1.79). The predictive ability for MPR (C-index=0.69 (95% CI 0.61-0.77) was better than for MBF (C-index=0.63 (95% CI 0.54-0.73) when predicting death, but both variables had similar predictive ability for the death or MACE (0.68 (95% CI 0.64-0.73) MBF vs. 0.68 (95% CI 0.64-0.72) MPR). A sensitivity analysis did not

indicate any bias caused by low event rates. Kaplan Meier survival estimate curves for MBF and MPR are presented in Figure 3 (death) and figure 4 (MACE). Death or MI was associated with stress MBF and MPR, age, LGE and history of cancer. The adjusted HR for a 1 ml/g/min decrease in MBF was 2.32 (95% CI 1.43-3.77) and a 1 unit decrease in MPR was 2.63 (95% CI 1.70-4.10).

In total 266 patients (25.4%) had a regional perfusion defect on clinical read in a least one myocardial segment. Deaths were no different between patients with regional perfusion defects and “normal” (uniform) perfusion (14 (5.3%) vs 28 (3.6%), $P=0.276$), but MACE was higher (103 (39%) vs 71 (9.1%), $P<0.0001$). Mean global stress MBF and MPR were lower in the perfusion defect group (1.74 +/- 0.62ml/g/min vs 2.17 +/- 0.71ml/g/min, $P<0.0001$ and 2.14 +/- 0.75 and 2.59 +/- 0.81, $P<0.0001$ respectively).



A multivariate Cox regression analysis was also performed on patients with no regional perfusion defects. Death was associated with, age, EF, history of cancer, history of hypertension and MPR, but not stress MBF. MACE was associated with age, a history of cancer and both stress MBF and MPR. The adjusted HR for a 1 unit decrease in MPR was similar to the whole cohort: 2.22 (95% CI 1.16-4.23) for death ($P=0.015$) and 1.65 (95% CI 1.14-2.38) for MACE ($P=0.008$) with stress MBF HR of 2.28 (95% CI 1.43-3.66) for MACE ($P=0.001$).

A further Cox regression analysis was performed excluding patients with previous CAD, MI or LGE. Death was associated with age, history of cancer, dyslipidemia and MPR. MACE was associated with age, a history of cancer and both stress MBF and MPR. The adjusted HR for a 1 unit decrease in MPR was 2.49 (95% CI 1.01-6.13) for death ($P=0.049$) and 2.38 (95% CI 1.30-3.77) for MACE ($P=0.003$) with stress MBF HR of 2.15 (95% CI 1.20-3.83) for MACE ($P=0.010$).

Discussion

This multicenter study, the largest quantitative perfusion CMR study to date, shows that myocardial stress MBF and MPR by CMR perfusion mapping are associated with adverse outcomes over and above other cardiovascular risk factors. This quantitation is possible in routine practice automatically at scale using an artificial intelligence based approach and these values are prognostic - a 1 SD increase in stress MBF (0.71ml/g/min) or MPR (0.82) is associated with a reduced risk of death by 36% and 52% and MACE by 54% and 37%, even after adjusting for other risk factors. The ease of measurement and quantitation makes this attractive both clinically and for research as an endpoint in studies exploring therapy to improve perfusion.

This study confirms the prognostic relevance of myocardial perfusion, which has previously been shown in PET studies (10–13). For example, Herzog and colleagues followed up 256 patients for a mean of 5.4 years (10). They found that even in patients with no perfusion defects, an abnormal MPR (<2) was associated with worse outcomes. Perfusion CMR has several additional benefits. Firstly, the spatial resolution is superior to other functional imaging modalities, reducing partial volume effects and improving the detection of perfusion abnormalities. CMR also does not use ionizing radiation which is advantageous particularly for repeat studies. Furthermore, following perfusion, late gadolinium enhancement images are acquired which allows direct comparison of ischemia and infarction and allows the operator to discriminate between reversible and “matched” perfusion defects corresponding to infarct.

The quantitative approach here, perfusion mapping, has already been validated against both rubidium PET (20), and invasive coronary physiology (22). Engblom et al recruited patients with stable CAD for PET and CMR perfusion on the same day. They showed that there was a

good correlation with global ($r=0.92$) and regional flow ($r=0.83$) (20). Kotecha et al studied invasive coronary physiology with FFR and IMR. They found that myocardium supplied by coronary arteries with FFR positive lesions had significantly lower MBF and MPR than remote myocardium and that myocardium supplied by FFR negative, IMR positive lesions had intermediate perfusion (22). Brown et al found that the repeatability of perfusion mapping is similar to the published PET literature in a cohort of healthy volunteers (19). Our study adds weight to those validations by additionally demonstrating prognostication.

There has been one previous fully quantitative perfusion outcome CMR study, a single-center dual bolus study of 395 patients followed for a median 460 days. This found that decreased myocardial perfusion reserve, determined by a set threshold (1.5) of MPR for ischemia per segment with total number of segments summed, contained prognostic information for a composite MACE endpoint. (32)

The current study exploits recent CMR technical developments via a clinically feasible dual sequence approach with a pixel-wise, rather than segmental approach, and full automation of analysis making a multicenter approach with 3.5x greater follow-up (1735 patient-years) feasible. It has also permitted the prognostic significance of MPR and MBF to be explored independently of other factors with multivariate modeling, placing CMR on the same footing as PET for ease of full blood flow quantification. For the first time we have shown that automatically derived MBF and MPR have prognostic relevance beyond the detection of regional ischemia. This provides the opportunity for quantitative perfusion analysis to be applied in the routine clinical setting to potentially risk stratify beyond the detection of regional ischemia alone. The predictive power is moderate but incremental over conventional factors.

With a relatively small number of events, our finding that MPR may be superior to stress MBF in predicting death but not death or MACE should not be over-stated. However, PET studies have also suggested MPR is a stronger predictor of cardiovascular mortality than maximal MBF. For example, Gupta et al. found that CFR was a stronger predictor of cardiovascular death than MBF in a study of 4029 patients with a median 5.6 year follow up (33). Patients with impaired CFR and MBF had the worst prognosis and the best outcome was when CFR and MBF were both normal. When the MBF was abnormal but the CFR normal, the event rate was very low. Conversely when the MBF was normal but CFR abnormal, the risk was intermediate. Explanations for this have been suggested. For example, it has been suggested that CFR / MPR may be measuring the vasodilator capacity which may be more important than peak MBF. An alternative suggestion is that there are biases and systematic errors in the stress and rest MBF which are eliminated when measuring MPR. Another potential confounder is the most common tracer used in the studies is rubidium in which the extraction fraction is lower than ^{15}O -water PET and this might affect precision at hyperemic flow measurements.

The mechanism for impaired myocardial perfusion contributing to worse outcomes is likely to be a combination of epicardial coronary disease and microvascular dysfunction. Standard perfusion images rely on the assumption that there is a “normal vessel” that supplies the reference myocardium. This may result in the underestimation of impaired perfusion, which may contribute to poor outcome even in patients without perfusion defects. In diffuse epicardial disease the ability for vasodilation may be impaired which can cause a continuous pressure fall along an artery likely contributing to ischemia in the absence of focal disease on angiography (34). Also, impaired perfusion in the absence of significant epicardial disease has been associated with increased microvascular resistance due to microvascular dysfunction (22,35). In

our cohort, patients with lower MBF and MPR had more cardiac risk factors. This suggests that these conditions are associated with an impairment of myocardial perfusion. Whether MACE is associated with microvascular or macrovascular disease or a combination of both in our cohort is unclear.

Limitations

With the relatively low event rate and large number of covariates, there is a potential for bias in the estimated coefficients. However, a sensitivity analysis using Firth's penalized model was used to check for bias. The conclusions were the same for both models making this bias unlikely. This is an observational trial and as such the associations reported do not necessarily imply causation. Although a number of potential confounders were adjusted for it is possible that an unmeasured or incompletely accommodated confounding factor may have influenced the results. Furthermore, as the study used electronic documentation to acquire outcome data, it is possible that a small number of events were missed. These limitations are consistent with previous perfusion outcome studies. We did not include cause of death in this study because this was not available from the United Kingdom Office for National Statistics, and may be prone to misclassification bias. Myocardial perfusion is likely to be more strongly associated with cardiovascular causes of death than all-cause mortality as used in this study. Although the perfusion mapping technique is robust, there were errors in 1.1% of cases. Errors can occur due to failures with motion correction, incorrect identification of the LV blood and mis-triggering. However, quality control images (such as blood pool identification, AIF graphs, and heart rate triggers) are outputted on the scanner in addition to the perfusion maps. This enables the clinician to have confidence in the quality of data used to produce the map.

Conclusion

Quantitative CMR perfusion mapping with automatic inline flow measurement using an artificial intelligence approach, permits the clinical use of myocardial perfusion at scale. Here in a two-center outcome study, the largest such study to date, both stress MBF and MPR were associated with death and MACE independently of other clinical risk markers. This provides the basis to use routinely acquired MBF and MPR to target therapy, which will require validation in prospective randomized controlled trials.

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Disclosures

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Table 1. Baseline demographics, cardiovascular magnetic resonance (CMR) parameters and outcomes of the studied population.

	N = 1049
<i>Demographics</i>	
Age (years)	60.9 +/- 13
Sex n (% male)	702 (70)
<i>Co-morbidities</i>	
Hypertension, n (%)	630 (60.1)
Dyslipidemia, n (%)	510 (48.6)
Diabetes Mellitus, n (%)	298 (28.4)
Previous PCI / CABG, n (%)	319 (30.4)
AF, n (%)	141 (13.4)
Stroke / TIA, n (%)	63 (6.0)
Smoking history, n (%)	360 (34.3)
Cancer, n (%)	108 (10.3)
<i>CMR parameters</i>	
LVEDV, ml	157 +/- 52.2
LV mass, g	119 +/- 38.4
EF, %	60. +/- 13.4
Infarct pattern LGE, n (%)	309 (29.5)
Non-infarct pattern LGE, n (%)	133 (12.7)
Stress MBF (ml/g/min)	2.06 +/- 0.71
MPR	2.48 +/- 0.82
<i>Outcome</i>	
Death, n (%)	42 (4.0)
MACE, n (%)	174 (16.6)
Myocardial infarction, n (%)	28 (2.7)
Stroke, n (%)	10 (0.95)
Heart failure admission n, (%)	18 (1.7)
Late revascularization, n (%)	127 (12.1)

Abbreviations: Percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), atrial fibrillation (AF), transient ischemic attack (TIA), left ventricle end-diastolic volume (LVEDV), ejection fraction (EF), late gadolinium enhancement (LGE), myocardial blood flow (MBF), myocardial perfusion reserve (MPR).



Table 2. A comparison between patients who had died or had a major adverse cardiovascular event (MACE) to those that did not.

	MACE N=174	No MACE N=875	Significance (p-value)
<i>Demographics</i>			
Age (years)	65.88 +/- 10.21	59.88 +/- 13.14	<0.0001
Sex n (% male)	136 (78.2)	566 (64.7)	0.001
<i>Co-morbidities</i>			
Hypertension, n (%)	131(75.3)	499 (57.0)	<0.0001
Dyslipidemia, n (%)	109 (62.6)	401 (45.8)	<0.0001
Diabetes Mellitus, n (%)	73 (42.0)	225 (25.7)	<0.0001
Previous PCI / CABG, n (%)	71 (40.8)	248 (28.3)	0.002
AF, n (%)	22 (12.6)	119 (13.6)	0.808
Stroke / TIA, n (%)	17 (9.8)	46 (5.3)	0.034
Smoking history, n (%)	74 (42.5)	286 (32.7)	0.014
Cancer, n (%)	24 (13.8)	84 (9.6)	0.102
<i>CMR parameters</i>			
LVEDV, ml	161.80 +/- 56.98	155.86 +/- 51.26	0.174
LV mass, g	129.01 +/- 41.93	117.05 +/- 37.40	0.0002
EF, %	56.88 +/- 15.58	60.83 +/- 12.78	0.002
Infarct pattern LGE, n (%)	94 (54.0)	215 (24.6)	<0.0001
Non-infarct pattern LGE, n (%)	18 (10.3)	115 (13.1)	0.382
Stress MBF (ml/g/min)	1.62 +/- 0.56	2.15 +/- 0.71	<0.0001
MPR	2.04 +/- 0.76	2.57 +/- 0.80	<0.0001

Abbreviations: Percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), atrial fibrillation (AF), transient ischemic attack (TIA), left ventricle end-diastolic volume (LVEDV), ejection fraction (EF), late gadolinium enhancement (LGE), myocardial blood flow (MBF), myocardial perfusion reserve (MPR).

Table 3. Cox proportional hazard models for a 1 ml/g/min decrease in stress myocardial blood flow (MBF) and 1 unit decrease in myocardial perfusion reserve (MPR).

Predictor			Death	Death and MACE
Stress MBF (ml/g/min)	Unadjusted	HR (95% CI) P value	2.28 (1.39-3.75) P=0.001	3.02 (2.34-3.89) P<0.0001
	Adjusted*	HR (95% CI) P value	1.93 (1.08-3.48) P=0.028	2.14 (1.58-2.90) P<0.0001
MPR	Unadjusted	HR (95% CI) P value	2.72 (1.70-4.39) P<0.0001	2.40 (1.91-3.01) P<0.0001
	Adjusted*	HR (95% CI) P value	2.45 (1.42-4.24) P=0.001	1.74 (1.36-2.22) P<0.0001

* models adjusted for age, sex, left ventricular (LV) end diastolic volume, LV mass, LV ejection fraction, late gadolinium enhancement, previous revascularization, diabetes, hypertension, dyslipidemia, stroke history, atrial fibrillation and cancer. Stress MBF and MPR are independently associated with death and major adverse cardiovascular events (MACE). Abbreviations hazard ratio (HR).



Circulation

Figure Legends

Figure 1. Automatic segmentation of the stress perfusion maps performed by machine learning with no user input. Base, mid and apical left ventricle short axis slices (left to right) for a 76-year-old male with dyslipidemia and no death or major adverse cardiovascular events (A) and a 64-year-old female with hypertension and atrial fibrillation who died within 24 months of the scan (B). Mean stress myocardial blood flow was 2.25ml/g/min in (A) and 1.52ml/g/min (B).

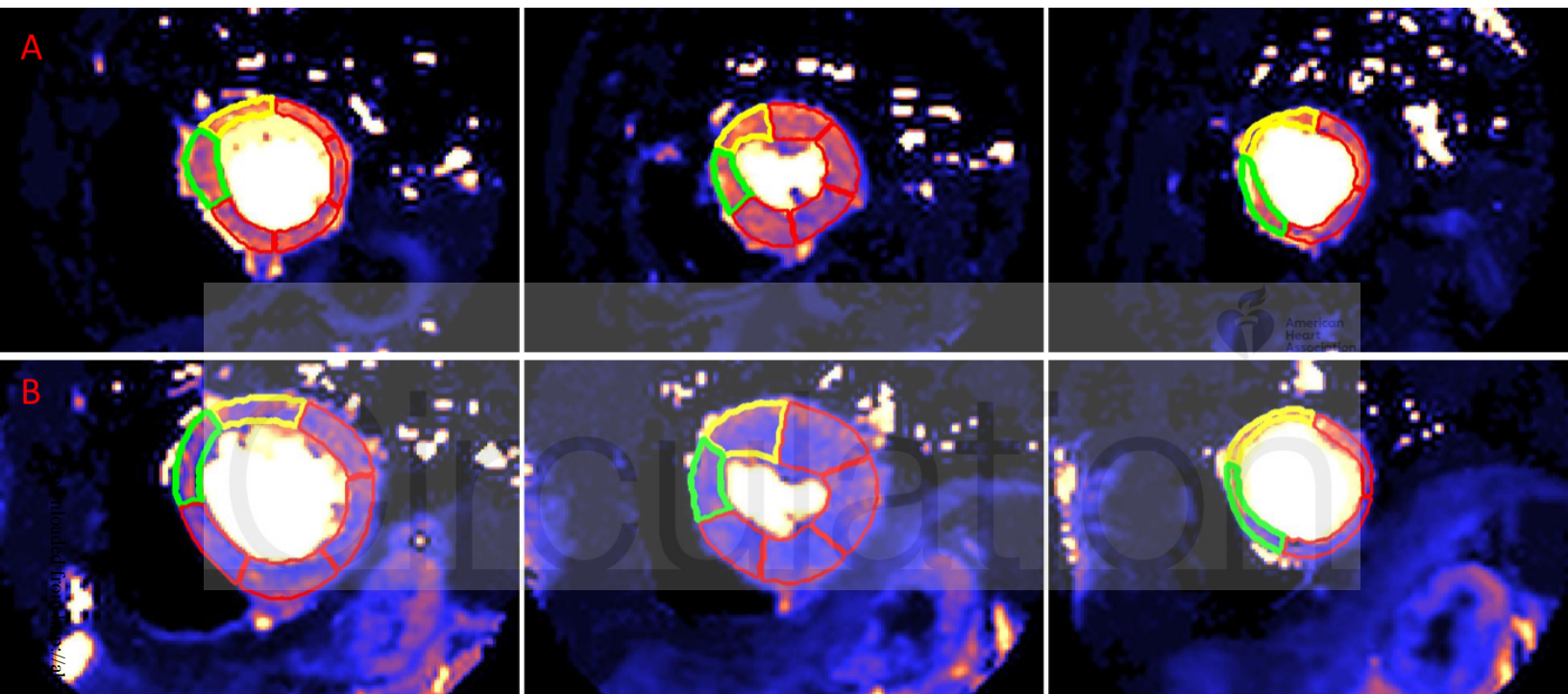
Figure 2. Study flow chart. 1049 patients were included in the final analysis. 143 patients met the exclusion criteria, there were reconstruction errors in perfusion maps in 15 cases and there were 45 cases of inadequate stress (no splenic switch off). 104 patients were lost to follow up. There were 188 events in total (MACE) in 174 patients including 42 deaths. Abbreviations: MACE- Major adverse cardiovascular events.

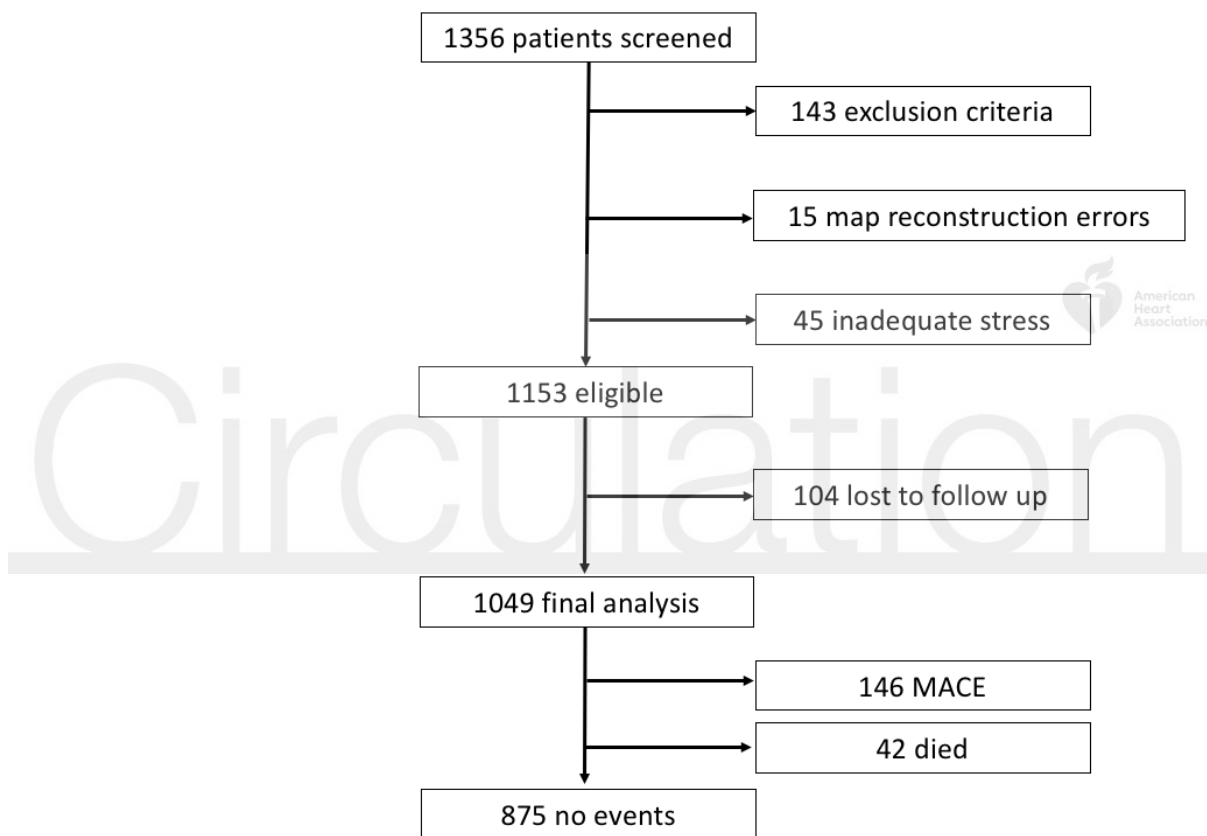
Figure 3. Kaplan Meier survival estimate curves for stress myocardial blood flow (MBF, A and B) and myocardial perfusion reserve (MPR, C and D). The red lines demonstrate the survival curves for the highest 50th percentile and the blue lines demonstrate the lowest 50th percentile of patients. B and D are magnified to highlight the separation of the curves. Rates of death are higher with impaired perfusion. Compared to patients in the highest 50th percentile, the patients in the lowest 50th percentile of MBF and MPR had higher rates of death (P=0.032 and P=0.01 respectively).

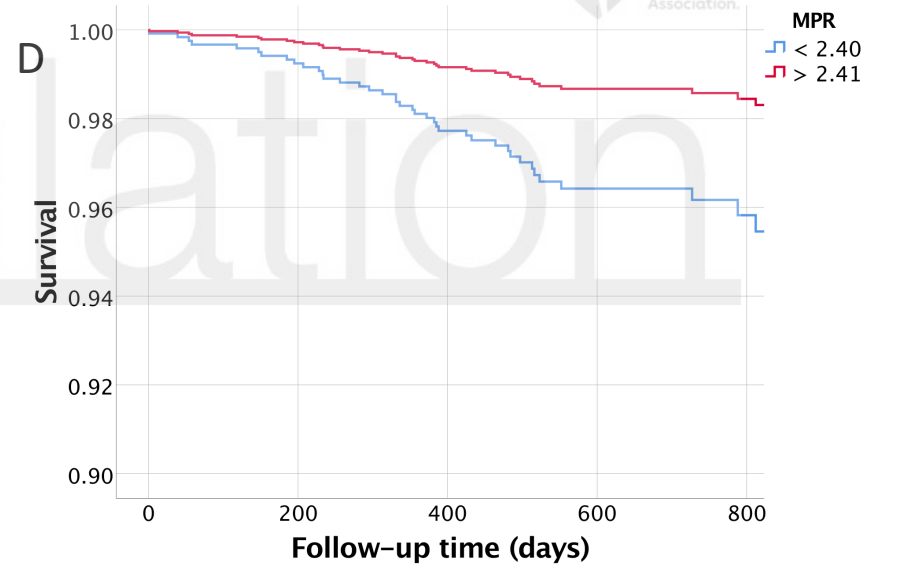
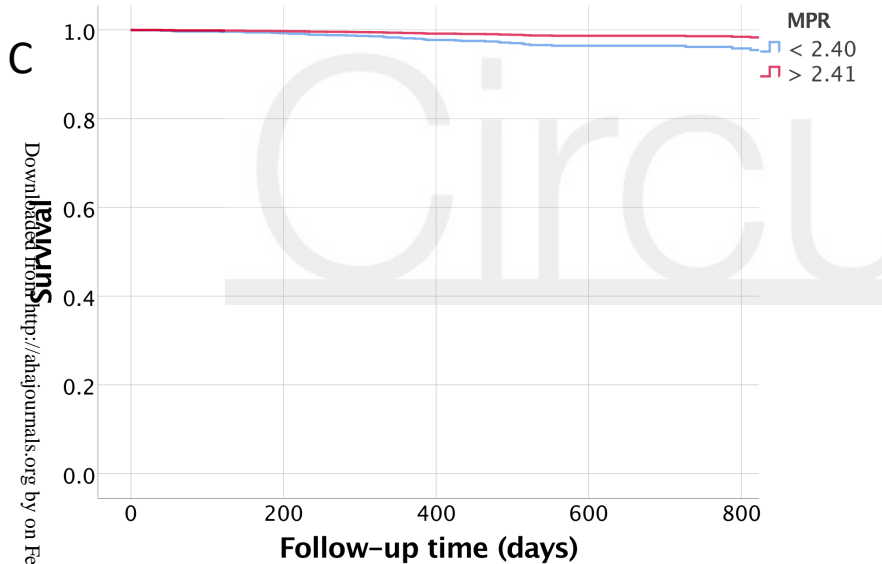
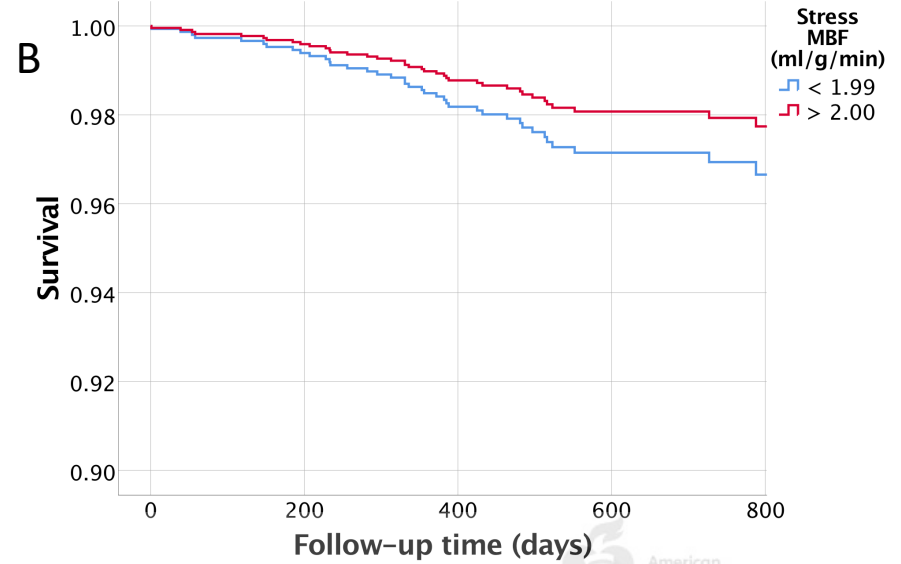
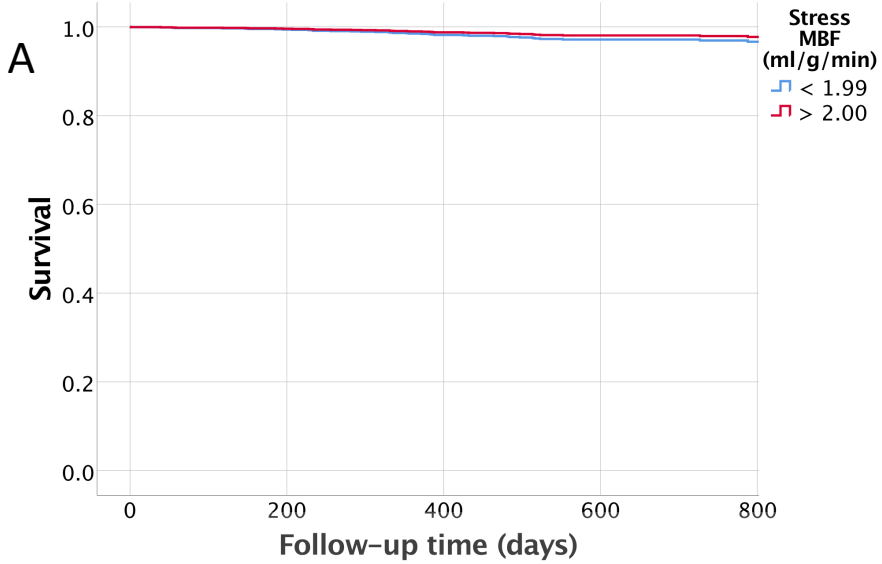
Figure 4. Kaplan Meier survival estimate curves demonstrating major adverse cardiovascular events (MACE) for stress myocardial blood flow (MBF, A), and myocardial perfusion reserve (MPR, B). The red lines demonstrate the survival curves for the highest 50th percentile and the blue lines demonstrate the lowest 50th percentile of patients. Compared to patients in the highest 50th percentile, the patients in the lowest 50th percentile of MBF and MPR had higher rates of death ($P < 0.001$ for both).



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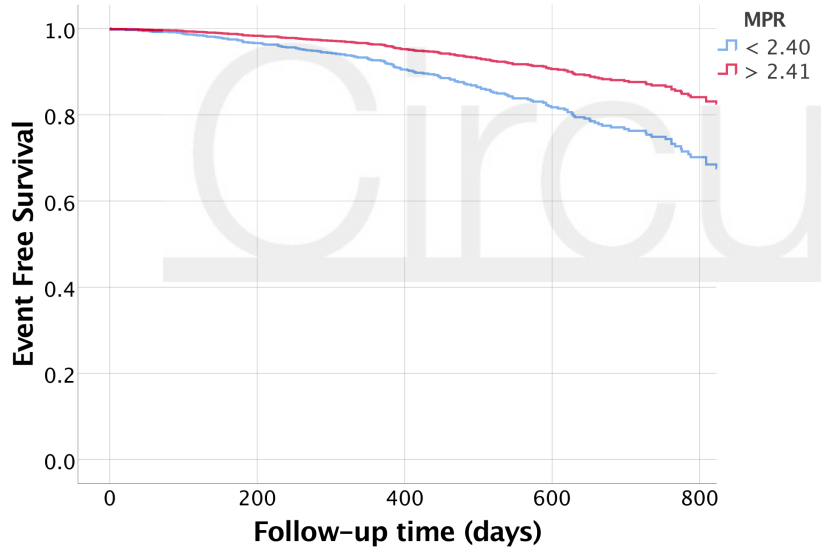
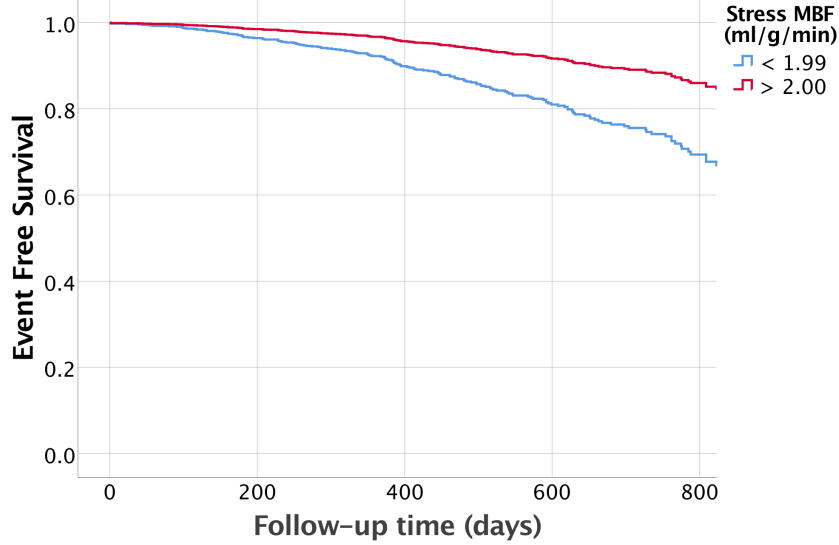




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		Time (days)				
		0	200	400	600	800
Number at risk	MBF <1.99	525	518	459	264	135
	MBF >2.00	524	521	460	269	143
	MPR <2.40	510	501	443	252	130
	MPR >2.40	508	507	448	265	138

A



Circulation

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		Time (days)				
		0	200	400	600	800
Number at risk	MBF <1.99	525	478	337	179	61
	MBF >2.00	524	501	373	179	63
	MPR <2.40	510	466	331	161	57
	MPR >2.40	508	484	361	182	59