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Doppler Versus Thermodilution-derived Coronary Microvascular Resistance to Predict Coronary Microvascular Dysfunction in Patients with Acute Myocardial Infarction or Stable Angina Pectoris

Running title: hMR Versus IMR Predicting Microvascular Dysfunction

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Abstract

Coronary microvascular resistance is increasingly measured as a predictor of clinical outcomes, but there is no accepted gold-standard measurement. We compared the diagnostic accuracy of two invasive indices of microvascular resistance, Doppler-derived hyperemic microvascular resistance (hMR) and thermodilution-derived index of microcirculatory resistance (IMR), at predicting microvascular dysfunction. 54 patients (61±10 years) undergoing cardiac catheterization, for stable coronary artery disease (n=10) or acute myocardial infarction (AMI, n=44), had simultaneous intracoronary pressure, Doppler flow velocity and thermodilution flow data acquired from 74 unobstructed vessels, at rest and hyperemia. Three independent measures of microvascular function were assessed, using predefined dichotomous thresholds: i) CFR, the average value of Doppler- and thermodilution-derived coronary flow reserve (CFR), and cardiovascular magnetic resonance derived: ii) Myocardial Perfusion Reserve Index (MPRI) and iii) Microvascular Obstruction (MVO). hMR correlated with IMR (rho = 0.41, p<0.0001). hMR had better diagnostic accuracy than IMR to predict CFR (area under curve, (AUC) 0.82 versus 0.58, p<0.001, sensitivity/specificity 77/77% versus 51/71%) and MPRI (AUC 0.85 versus 0.72, p=0.19, sensitivity/specificity 82/80% versus 64/75%). In AMI patients, the AUCs of hMR and IMR at predicting extensive MVO were 0.83 and 0.72 respectively (p=0.22, sensitivity/specificity 78/74% versus 44/91%). We measured two invasive indices of coronary microvascular resistance to predict multiple distinct measures of microvascular dysfunction. We found these two invasive indices only correlate modestly and so cannot be considered equivalent. In our study, the correlation between independent invasive and non-invasive measures of microvascular function was better with hMR than with IMR.

Key words: Coronary microvascular resistance; myocardial infarction; hyperemic microvascular resistance (hMR); index of microcirculatory resistance (IMR)

Introduction

Up to 50% of patients have microvascular obstruction (MVO) [1] post primary percutaneous coronary intervention (PPCI), resulting in worse clinical outcomes. [2] MVO reflects microvascular dysfunction (MVD) due to distal embolization of thrombus, endothelial dysfunction, reperfusion injury and intramyocardial hemorrhage.[3] MVD also indicates an adverse prognosis in the setting of stable coronary artery disease.[4] Elevated coronary microvascular resistance (MVR) is the hallmark of MVD. Two invasive indices of MVR are now described. Both derive MVR from simultaneous distal coronary artery measurements of pressure and flow during hyperemia using intra-coronary guidewires. However, the index of microcirculatory resistance (IMR) [5] estimates flow with thermodilution, whereas hyperemic microvascular resistance (hMR) measures Doppler-flow velocity.[6] Both indices have separately been shown to predict infarct size,[7, 8] MVO,[8] regional wall motion [7] and adverse LV remodeling.[7] However to date, no study has compared hMR and IMR against invasive and non-invasive measurements of MVD in humans. Our study aims were to determine the level of agreement between IMR and hMR across a range of MVR and to compare the ability of IMR and hMR to predict independent invasive and non-invasive measures of MVD.

Methods

In this prospective, two-centre study, patients undergoing coronary angiography were enrolled at St. Thomas Hospital, London, United Kingdom and the VU University Medical Centre, Amsterdam, The Netherlands. To sample a wide range of MVR, we enrolled two groups: those with stable angina and those presenting with an AMI, defined as a cardiac biomarker elevation in association with characteristic electrocardiographic (ECG) changes and/or typical symptoms. In AMI patients measurements were made in the infarct artery following PCI and in an angiographically normal reference artery when feasible. Exclusion criteria were hemodynamic instability or cardiogenic shock, significant LV dysfunction, previous coronary artery bypass grafting, severe comorbidity, left main stem disease, and standard contraindications to CMR. The protocols were approved by NRES London Westminster Medical Ethics Review Committee and the IRB of VU University Medical Centre in Amsterdam. All patients were asked to give written informed consent.

Measurements were taken in coronary arteries without hemodynamically significant coronary artery disease (defined as fractional flow reserve (FFR) > 0.80), or immediately following successful PCI in patients with a significant coronary artery stenosis. After calibrating and normalising to aortic root pressure through a 6F-guiding catheter, a 0.014-inch dual pressure and Doppler flow-velocity tipped sensor guidewire (ComboWire Guidewire, Phillips Volcano, San Diego, USA) and a 0.014-inch Pressure Wire® (with temperature thermistors on the distal shaft and tip: St Jude Medical, St. Paul, Minnesota, USA) were advanced to the distal vessel (>5cm from the coronary ostia). The pressure transducers of each wire were positioned adjacent to each other (Fig. 1B). The following measurements were taken after administration of intracoronary nitrates (200-300 mcg): aortic pressure (P_a), distal coronary artery pressure (P_d), Doppler-derived average peak velocity (APV) and thermodilution-derived transit mean time (T_{mn}). [5, 9] Measurements were taken at rest and during peak hyperemia with intravenous adenosine (140 mcg/kg/min). The following were then calculated as previously described: in all patients FFR,[10] hMR,[11] IMR,[5] and Doppler-[12] and thermodilution-derived CFR,[9] and in AMI patients corrected TIMI frame count.[13] Doppler-flow velocity tracings of insufficient quality were discarded from analysis. CFR was then calculated as the average of Doppler-derived CFR and thermodilution-derived CFR. Investigators performing data analyses were blinded to all clinical data. CMR scans were performed using either a 3-Tesla MR-scanner (St Thomas' Hospital, London: Achieva, Phillips Healthcare, Best, Netherlands) or 1.5-Tesla MR-scanner (VU University Medical Centre, Amsterdam: Magnetom Avanto, Siemens, Erlangen, Germany). Cine images were acquired in 2-, 3-, and 4-chamber orientations and in a whole LV short-axis stack using a steady-state free precession sequence. CMR high-resolution stress (adenosine 140mcg/kg/min for 4 minutes) and rest perfusion scans were performed exclusively on a 3-Tesla MR-scanner, within 48 hours of MVR measurements, using gadolinium contrast. In AMI patients late gadolinium enhancement images were obtained 15 minutes following the last CMR contrast injection. Left ventricular (LV) ejection fraction and LV mass were calculated from cine images. The myocardial perfusion reserve index (MPRI) was derived from semi-quantitative perfusion analysis as previously described, to provide territory specific values to match invasive data, using a 16-segment American Heart Association model (Fig. 7 online data supplement).[14] Microvascular obstruction was manually delineated from late gadolinium

enhancement images as an area of hypoenhancement within infarcted LV mass (Fig. 1D).[15] Extensive MVO was a pre-defined dichotomous variable when there was > 2ml MVO volume present.[16] Further details on the methods can be found in the online data supplement.

Statistical analyses were performed using GraphPad Prism 6.0 (GraphPad, San Diego, USA) and MedCalc Statistical Software version 12.7.8 (MedCalc Software, Ostend, Belgium). Continuous variables were tested for normality using the Shapiro–Wilk test and presented as mean ± SD when data were normally distributed or as median with interquartile range when data were non-normally distributed. Correlations between hMR and IMR, and each with CFR, MPRI and MVO were assessed using Spearman's (rho) analyses. MVD was defined dichotomously for each independent outcome variable: CFR <2.0,[17] MPRI< 1.0,[14, 18] and extensive MVO.[16] Receiver-operator characteristic (ROC) analysis was performed to determine the best cut-off values for predicting MVD using each method, and comparisons made using the DeLong method. P values of <0.05 were considered significant.

Results

The flow of patients through the study is shown in Fig. 2. Two patients (4%) were excluded due to poor quality Doppler traces, leaving 54 patients (10 stable angina patients and 44 AMI patients: 33 with STEMI; 11 with non-STEMI) with 74 complete invasive physiology datasets (Table 1). Invasive and CMR physiological data was acquired in 40 patients (Table 2: 8 stable angina patients and 32 AMI patients: 27 with STEMI; 5 with non-STEMI). The time between invasive measurements and CMR scans was 24 hours (7-49hours). In the enrolled population (see table 1), hMR was 2.60 (1.99, 3.43) mmHg·cm^{-1}·sec and IMR was 19.0 (13.0, 29.8) U. hMR significantly correlated with IMR (Fig. 3: rho=0.39; p=0.0006). Baseline and hyperemic thermodilution T_{mn} values were 0.56 (0.35, 0.92) seconds and 0.27 (0.18, 0.39) seconds respectively. Baseline and hyperemic Doppler APV values were 15.3 (12.0, 20.7) cm^{-1}.s and 29.4 (21.5, 37.6) cm^{-1}.s respectively. Tmn values correlated significantly APV values at baseline (rho=-0.36; p=0.002) and hyperemia (rho=-0.41; p=0.0003). There was a strong correlation between Doppler-derived CFR 1.90 (1.46, 2.21) and thermodilution-derived CFR 1.82 (1.50, 2.47) (rho=0.61; p<0.0001).

hMR and IMR correlated with CFR (hMR, rho=-0.52 p<0.0001; IMR, rho=-0.24 p=0.04). hMR values were higher in patients with MVD defined dichotomously by CFR (3.16 versus (vs.) 2.12

mmHg·cm^{-1}·sec, p<0.0001: Fig. 6A), but there was no difference between groups using IMR (22 vs. 19 U, p=0.25: Fig. 6A). Delong ROCanalysis demonstrated that hMR had superior diagnostic accuracy compared with IMR at predicting MVD: area under curve (AUC) 0.82 vs. 0.58, p<0.001 (Fig. 4). A threshold of ≥ 2.5 mmHg·cm^{-1}·s for hMR provided the highest sensitivity (0.77) and specificity (0.77) for detecting MVD, while the optimal threshold for IMR was ≥ 21.5 U, with sensitivity of 0.51 and specificity of 0.71.

hMR was significantly correlated with MPRI (rho=-0.58; p<0.001) but IMR was not (rho=-0.27; p=0.15). hMR and IMR values were higher in patients with MVD, defined dichotomously by MPRI (hMR: 3.43 vs. 2.11 mmHg·cm^{-1}·sec, p<0.001, IMR: 27.0 vs. 18.4 U, p=0.02: Fig. 6B). ROC analysis showed hMR had numerically superior diagnostic accuracy over IMR to predict MPRI, although the difference did not reach statistical significance (AUC, 0.85 vs. 0.72, p=0.19) (Fig. 5 (A). A threshold of ≥ 2.5 mmHg·cm^{-1}·s for hMR provided the optimal sensitivity (0.82) and specificity (0.80) for predicting MVD. The best cut off value for IMR was ≥ 24.0 U, with poorer sensitivity (0.64) and specificity (0.75).

In the AMI patients with invasive and CMR data (see Fig. 2), MVO was visible in 42% of patients. In these patients MVO volume was 3.2 mls (2.0, 5.2). Both infarct-related artery hMR and IMR measurements correlated with MVO volume (hMR, rho=0.46 p=0.001; IMR, rho=0.36 p=0.01). hMR and IMR values were both significantly higher when there was evidence of extensive MVO (hMR 3.74 vs. 2.60 mmHg·cm^{-1}·sec, p=0.003; IMR 23.5 vs. 19.0 U, p=0.04: Fig. 6C). ROC analysis demonstrated that hMR had numerically superior diagnostic accuracy over IMR to predict the presence of extensive MVO (superior sensitivity), but this was not significant (AUC 0.83 vs. 0.72, p=0.22) (Fig. 5 (B). A threshold of ≥ 3.25 mmHg·cm^{-1}·s provided the highest sensitivity (0.78) and specificity (0.74) for detecting extensive MVO. The best cut off for IMR was ≥ 40 U with sensitivity (0.44) and specificity (0.91). In addition, hMR had superior diagnostic accuracy over IMR to predict the presence of any MVO, but this difference was not significant (AUC 0.75 vs. 0.66).

Discussion

To our knowledge, this is the first study in humans to have simultaneously assessed the correlation of two invasive indices of MVR, Doppler-derived hMR and thermodilution-derived IMR,

against each other and against independent measures of MVD. The main findings of this study are: (1) hMR and IMR correlate modestly with each other, and therefore cannot be considered equivalent predictors of MVD; (2) hMR had superior diagnostic accuracy over IMR to predict MVD determined invasively by CFR; (3) hMR had clinically superior sensitivity over IMR to predict MVD determined by cardiac magnetic resonance derived MPRI and extensive MVO, but there were no statistically significant differences observed; (4) an hMR threshold of ≥2.5 mmHg·cm^{-1}·s and an IMR threshold between 21.5 and 24 U were optimal for predicting MVD determined by CFR and MPRI; (5) in the infarct related artery following an AMI, an hMR threshold of ≥ 3.25 mmHg·cm^{-1}·s and an IMR threshold of ≥ 40 U were optimal for predicting MVD determined by extensive MVO.

Optimal assessment of MVD enables better risk stratification for adverse cardiovascular outcomes. In addition, in the setting of AMI post PPCI, instant MVR measurement could help select patients most likely to benefit from adjunctive pharmaco-therapy (e.g. intracoronary GpIIbIIIa inhibitors[19, 20]). Accurate assessment of MVR can be performed safely in the cardiac catheter laboratory, across a broad spectrum of MVD in AMI and stable angina patients, using either hMR or IMR. However, although equivalent hyperaemic distal pressures were obtained from the two intracoronary guidewires, overall correlation between hMR and IMR was far from strong (rho=0.39). Therefore discrepancies in the MVR measurements relate to differences in the estimation of flow. Each technique has inherent theoretical assumptions that are challenged in varying pathophysiological states. Thermodilution derived transit time is a surrogate of absolute coronary blood flow and is not indexed to the amount of myocardium subtended. Doppler flow velocity however decreases only by a fraction as branching occurs and therefore precise positioning within the distal vessel is less important as long as a good Doppler flow trace is obtained (~5 minutes).

Previous investigators have reported a wide range of prognostic thresholds for both hMR (2.5 to 3.6 mmHg·cm^{-1}·s[16]) and IMR (32 to 40[7, 21]), in patients who have suffered a recent AMI. The thresholds we identified for hMR and IMR to predict the presence of MVO are similar to that previously reported.[8, 16, 22] The thresholds for predicting MVD with CFR and MPRI, which are more sensitive measures of MVD, are understandably lower for both hMR and IMR. Recently Patel et al measured hMR and IMR directly following PPCI in 34 patients recruited with ST-segment elevation

myocardial infarction.[23] They demonstrated that hMR had a superiority trend over IMR in predicting parameters of infarct size and impaired left-ventricular ejection fraction, but this failed to reach statistical significance.[23] However they did not include measurements of MVD in this comparison.

Several study limitations should be acknowledged. First, notwithstanding the detailed physiological characterization of our study cohort, this is a study with a relatively small sample size. Second, there is currently no true reference standard measurement of microvascular function. In our study we used multiple distinct modalities of assessing microvascular function, which we believe represents the best available composite clinical surrogate for a true reference standard. CFR was chosen as the invasive measurement of MVD because it was readily obtainable in every patient, and is utilized in clinical practice as a marker of MVD (with CFR<2.0 in unobstructed coronary arteries, as pre-specified in our study).[17] A few investigators have used different CFR thresholds, namely 2.3 and 2.5. In our study, the performance of hMR was better than IMR (when comparing AUC) with either of these CFR thresholds. Third, whilst we acknowledge that CFR can be affected by several hemodynamic factors and loading conditions, these conditions were minimized by ensuring that: a) baseline and peak measurements for Doppler and thermodilution were taken immediately after each other, b) all hyperemic measurements were taken during steady state hyperemia with intravenous adenosine and c) no other drugs or intravenous fluids were administered between Doppler and thermodilution measurements. Fourth, CMR late gadolinium enhancement was performed up to 6 days post AMI and therefore the measurements may be confounded by partial resolution of transient MVD post AMI. Nevertheless, this would be expected to affect both hMR and IMR to the same extent. Finally, it should be noted that there is no accepted dichotomous threshold for defining MPRI and MVO and the values we have used may differ from some studies.

This prospective two-centre study assessed the correlation between Doppler-derived hyperemic MVR and thermodilution-derived index of microcirculatory resistance: against each other, and against independent reference measures of MVD. We found these two invasive indices are both predictors of MVD. However, only modest correlation was found between hMR and IMR| Therefore they cannot be considered equivalent predictors of MVD.

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Disclosures

Dr Perera, Dr van Royen and Dr de Waard have served as speakers or panelists in educational events organized by St Jude Medical and Volcano Corporation. Dr Perera and Dr van Royen have received educational grants from Volcano Corporation and St Jude Medical to support the respective ComboWires and Pressure wires used in this study. The other authors report no conflicts.

Figure Legends:

Fig. 1. Cardiac catheterization protocol used to derive invasive measurements of microvascular resistance.

(A) Combomap Console (Volcano® Corporation, San Diego, USA) displaying continuous aortic and distal coronary artery pressure (P_d) and Doppler flow velocity.

(B) Coronary angiographic image demonstrating a 0.014-in ComboWire (Volcano® Corporation, San Diego, USA) and a 0.014-in Pressure Wire® (St Jude Medical, Uppsala, Sweden) placed in equivalent positions in the distal circumflex artery.

(C) St Jude Console (St Jude Medical, Uppsala, Sweden) displaying aortic and distal coronary artery pressure (P_d), and three transit mean time (T_{mn}) measurements at both baseline and during steady state hyperemia.

(D) Late gadolinium enhancement cardiac magnetic resonance image 5 days after a revascularized acute ST-segment elevation myocardial infarction of the left anterior descending coronary artery. This short-axis view shows a hypo-enhanced core of microvascular obstruction (MVO) within a hyperenhanced area of infarcted tissue in the anteroseptal myocardium.

Fig. 2. Flow of patients through the study. Two patients (4%) were excluded due to poor quality Doppler traces, leaving 54 patients (10 stable angina patients and 44 acute myocardial infarction (AMI) patients: 33 with STEMI; 11 with non-STEMI) with 74 complete invasive physiology datasets (Table 1: those with a full hyperemic microvascular resistance, index of microcirculatory resistance and coronary flow reserve dataset from at least one vessel). Invasive and cardiovascular magnetic resonance (CMR) physiological data was acquired in 40 patients (Table 2: 8 stable angina patients and 32 AMI patients: 27 with STEMI; 5 with non-STEMI). 14 patients were excluded due to claustrophobia, patient preference (declined), being too obese to have a CMR scan (logistics), or due to poor quality perfusion data from an inadequate breath-hold. * = CMR infarct size and microvascular obstruction (MVO) measurements were obtained in all 32 AMI patients (27 with

STEMI; 5 with non-STEMI), whereas CMR perfusion was only performed on high-resolution 3-Tesla perfusion scans in 23 patients (8 stable angina patients and 15 AMI patients).

Fig. 3. Correlation of hyperemic microvascular resistance (hMR) versus the index of microcirculatory resistance (IMR).

Fig. 4. Performance of invasive indices of microvascular resistance versus an invasive standard of coronary microvascular dysfunction: receiver-operating characteristics analysis. Accuracy of hyperemic microvascular resistance (hMR) versus index of microcirculatory resistance (IMR) in predicting coronary flow reserve (CFR) < 2.0 in vessels with a fractional flow reserve of > 0.80. The optimal thresholds were ≥ 2.5 mmHg cm^{-1} s for hMR and ≥ 21.5 U for IMR.

Fig. 5. Performance of invasive indices of microvascular resistance versus non-invasive markers of coronary microvascular dysfunction: receiver-operating characteristics analysis. **(A)** Accuracy of hyperemic microvascular resistance (hMR) and index of microcirculatory resistance (IMR) in predicting myocardial perfusion reserve index <1.0, a non-invasive marker of coronary microvascular dysfunction. The calculated cut off values were ≥ 2.5 mmHg cm^{-1} s for hMR and ≥ 25 U for IMR. (**B)** Accuracy of hMR and IMR in predicting the presence or absence of extensive microvascular obstruction (> 2mls),[20] a non-invasive standard of coronary microvascular dysfunction in acute myocardial infarction. The best cut off values were ≥ 3.25 mmHg cm^{-1} s for hMR and ≥ 40 U for IMR.

Fig. 6. Hyperemic microvascular resistance (hMR) and index of microcirculatory resistance (IMR) invasively measured in patients with and without evidence of microvascular dysfunction: as evidenced by (A) invasive coronary flow reserve (CFR), (B) non-invasive myocardial perfusion reserve index (MPRI) and (C) non-invasive extensive microvascular obstruction (MVO). Boxes represent median and interquartile range with whiskers as the 10^{th} to 90^{th} percentile and values outside the 10^{th} to 90^{th} percentile are presented as individual data point.

Table 1. Clinical Demographics and Angiographic Characteristics of the 54 Patients

Variable	AMI Patients (n=44)	Angina Pectoris (n=10)
Men	40 (90)	9 (90)
Age (years)	60.2 ± 10.6	61.7 ± 9.0
Body Mass Index (kg/m$^{2)}$	26.9 ± 3.7	29.8 ± 3.4
Hypertension	29 (64)	7 (64)
Diabetes Mellitus	21 (47)	3 (27)
Hypercholesterolemia	36 (80)	9 (82)
Smoker	30 (67)	8 (73)
Non-culprit/Non-treated Measurements		
LAD / LC / Right	9 / 2 / 7	6 / 3 / 0
Fractional Flow Reserve	0.95 ± 0.06	0.89 ± 0.04
Culprit/treated Measurements		
LAD / LC / Right	24 / 7 / 10	3 / 0 / 3
Fractional Flow Reserve (post PCI)	0.93 ± 0.06	0.92 ± 0.05
Acute Myocardial Infarction Characteristics		
Corrected TIMI frame count	17 (10-26)	n/a
Peak Troponin T, μg/L	1075 (203-7189)	n/a

Data are number (%), mean±SD or median (IQR). LAD, left anterior descending; LC, left circumflex artery; PCI, percutaneous coronary intervention.

Table 2. Cardiac Magnetic Resonance (CMR) Data

Variable	All patients
Duration between invasive measurements and CMR, hours	24 (7, 49)
Semi-quantitative CMR analysis (31 datasets from 23 patients*)	
Myocardial Perfusion Reserve Index	1.07 (0.86, 1.49)
Volumetric analysis (40 datasets from 40 patients)	

Left Ventricular End Diastolic Volume, ml	174 (150, 200)
Left Ventricular End Systolic Volume, ml	81 (55, 119)
Left Ventricular Ejection Fraction, %	52 (41, 63)
Microvascular Obstruction (32 datasets from 32 patients)	
Evidence of Microvascular Obstruction, number	13
Evidence of extensive** Microvascular Obstruction, number	10
Quantitative infarct size analysis (32 datasets from 32 patients)	
Infarct Size, g	22.5 (5.1, 35.2)
Infarct Size % of Left Ventricular mass	14.3 (4.5, 24.8)

Data are number, median (interquartile range) or mean ± SD. * = includes MPRI values from corresponding culprit / non-culprit vessels. ** = more than 2mls volume.

Fig. 1 AJC hMR IMR_bestsetConverted.png

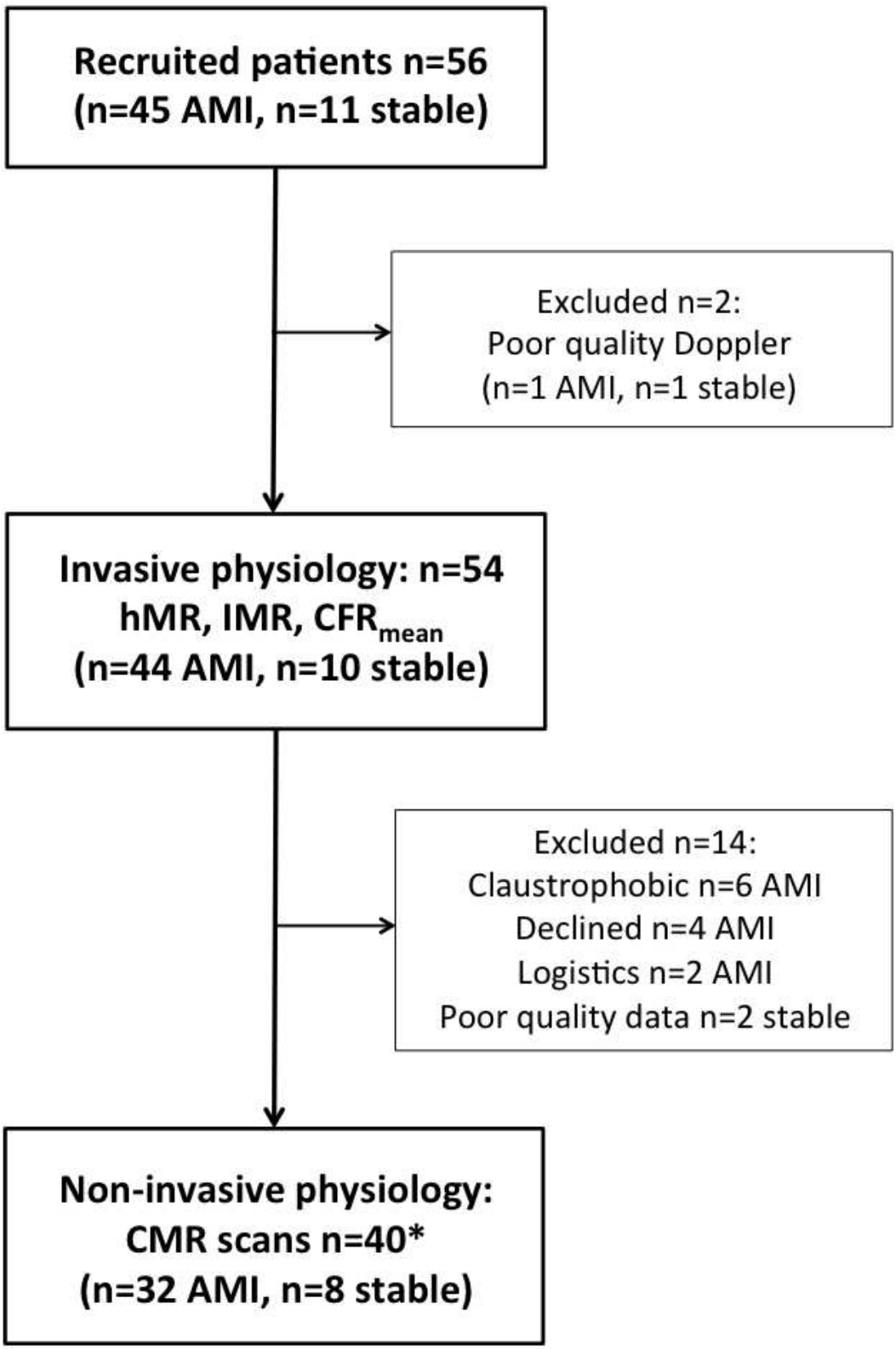

Fig. 2 AJC hMR IMR_bestsetConverted.png

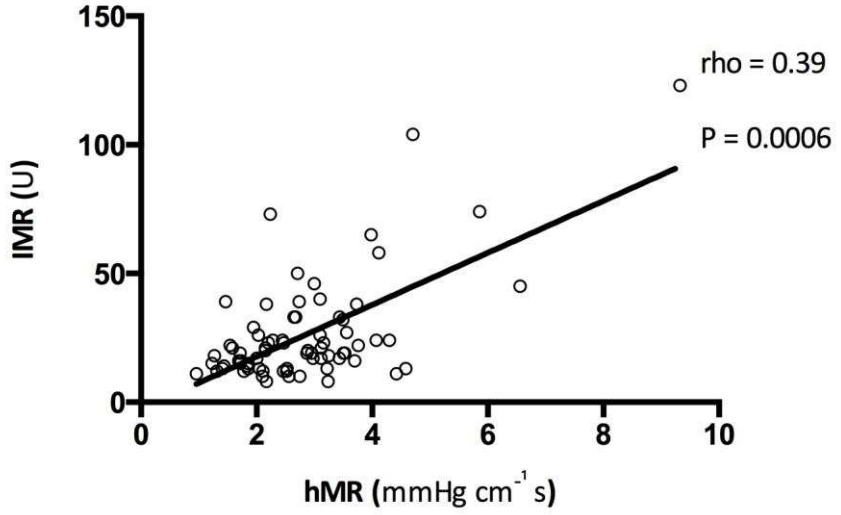

Fig. 3 AJC hMR IMR_bestsetConverted.png

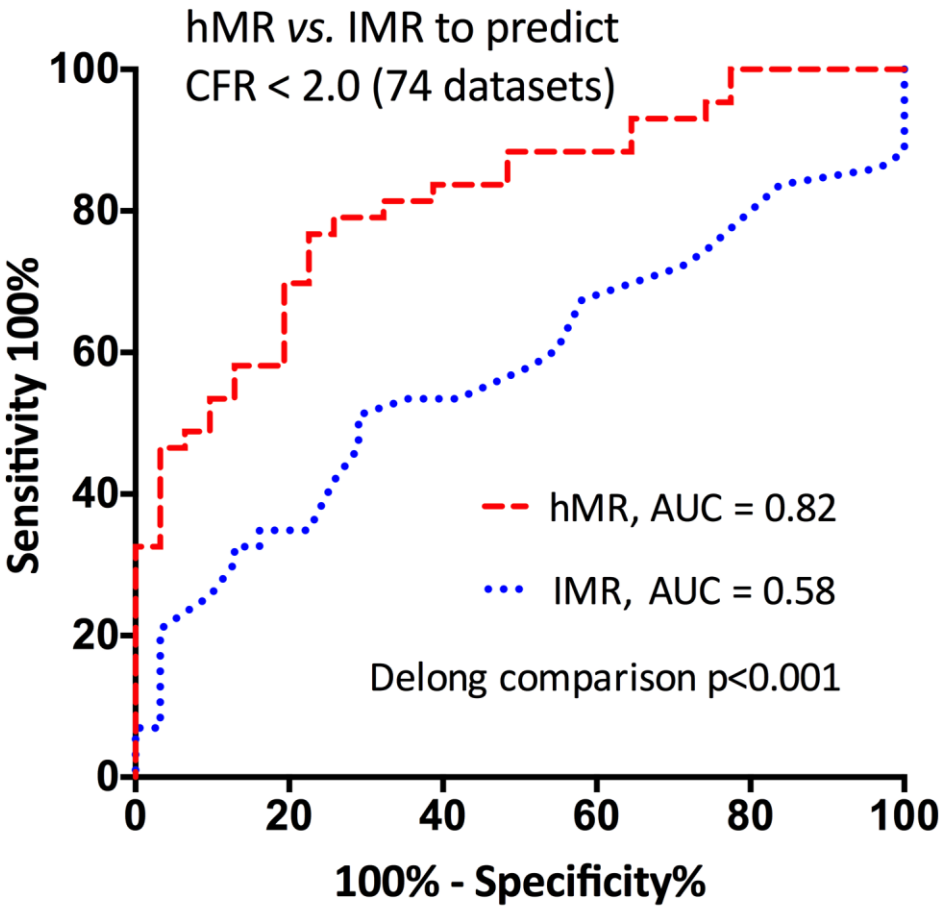

Fig. 4 AJC hMR IMR_bestsetConverted.png

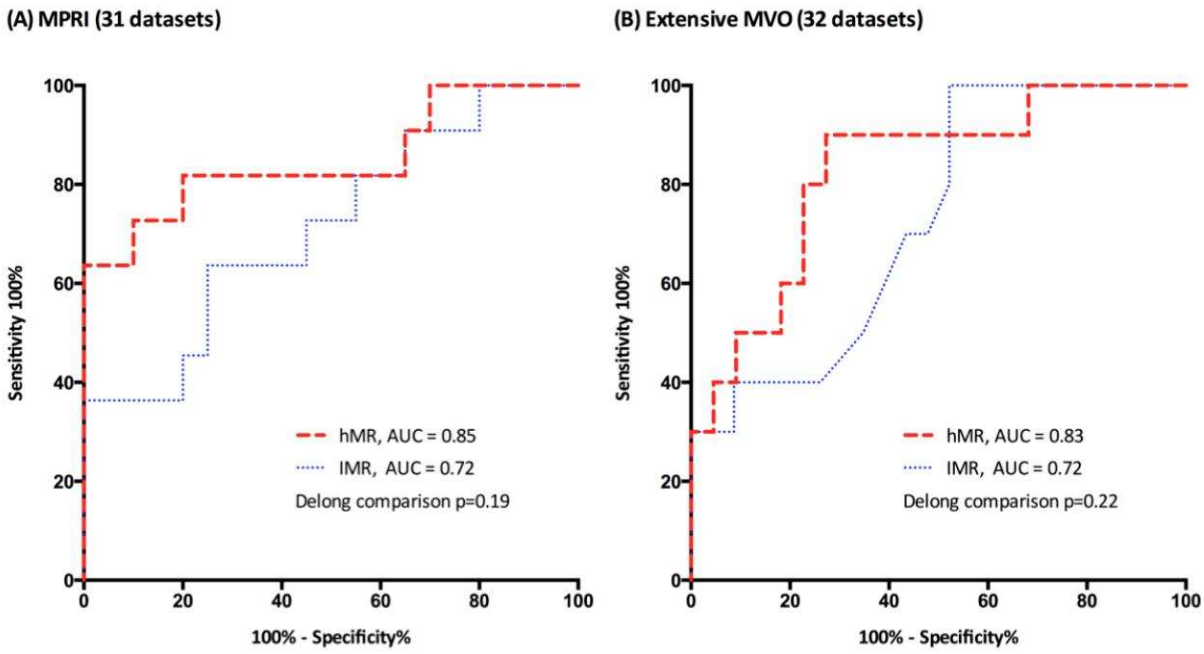

Fig. 5 AJC hMR IMR_bestsetConverted.png

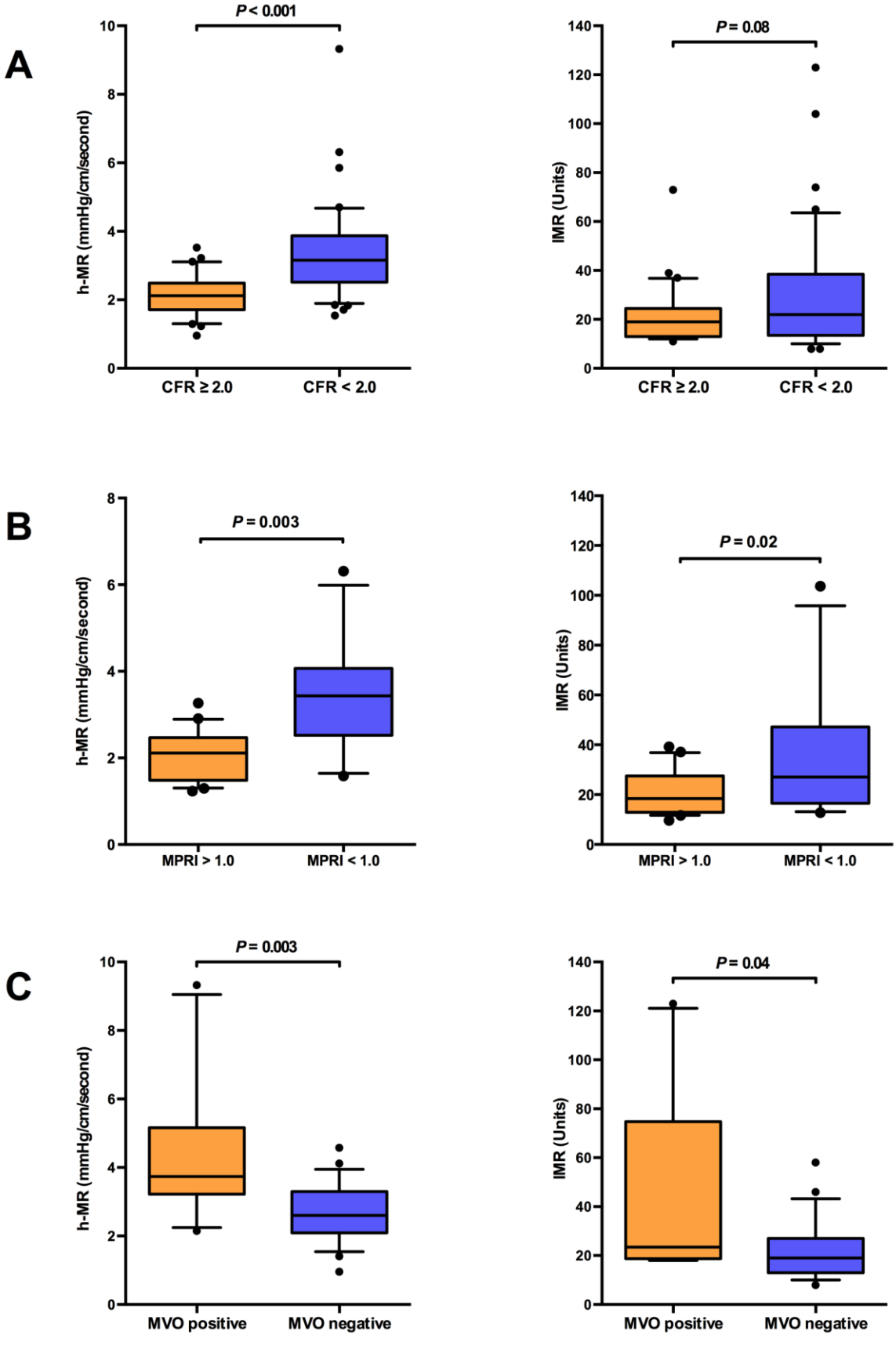

Fig. 6 AJC hMR IMR_bestsetConverted.png

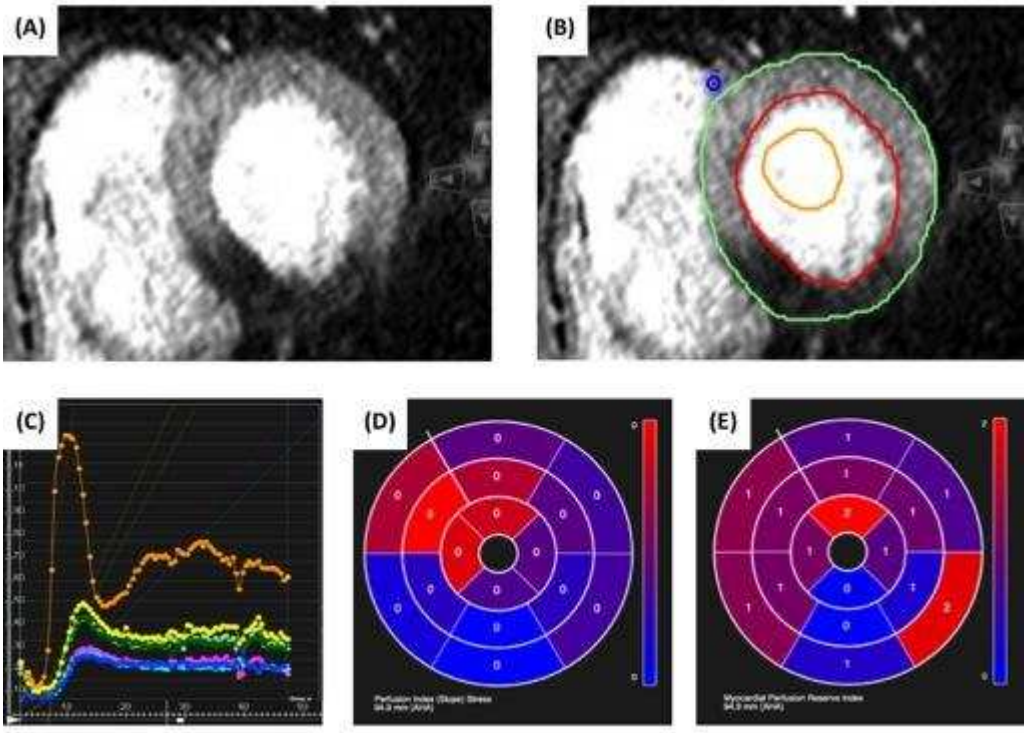

Fig. S1 AJC hMR IMR.jpg