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Myocardial Perfusion Pattern for Stratification of Ischemic Mitral Regurgitation Response to Percutaneous Coronary Intervention

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Abstract

Objective—Ischemic mitral regurgitation (MR) is common, but its response to percutaneous coronary intervention (PCI) is poorly understood. This study tested utility of myocardial perfusion imaging (MPI) for stratification of MR response to PCI.

Methods—MPI and echo were performed among patients undergoing PCI. MPI was used to assess stress/rest myocardial perfusion. MR was assessed via echo (performed pre- and post-PCI).

Results—317 patients with abnormal myocardial perfusion on MPI underwent echo 25±39 days prior to PCI. MR was present in 52%, among whom 24% had advanced (≥moderate) MR. MR was associated with LV chamber dilation on MPI and echo (both $p<0.001$). Magnitude of global LV perfusion deficits increased in relation to MR severity ($p<0.01$). Perfusion differences were greatest for global summed rest scores, which were 1.6-fold higher among patients with advanced MR vs. those with mild MR ($p=0.004$), and 2.4-fold higher vs. those without MR ($p<0.001$). In multivariate analysis, advanced MR was associated with fixed perfusion defect size on MPI (OR 1.16 per segment [CI 1.002–1.34], $p=0.046$) independent of LV volume (OR 1.10 per 10ml [CI 1.04–1.17], $p=0.002$). Follow-up via echo (1.0±0.6 years) demonstrated MR to decrease (≥1 grade) in 31% of patients, and increase in 12%. Patients with increased MR after PCI had more severe inferior perfusion defects on baseline MPI ($p=0.028$), whereas defects in other distributions and LV volumes were similar (p=NS).

Conclusions—Extent and distribution of SPECT-evidenced myocardial perfusion defects impacts MR response to revascularization. Increased magnitude of inferior fixed perfusion defects predicts post-PCI progression of MR.

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Keywords

mitral regurgitation; myocardial perfusion; SPECT

Introduction

Mitral regurgitation (MR) is present in approximately 20% of patients undergoing coronary revascularization, conferring increased risk for long-term morbidity and mortality [1–3]. Typically termed “ischemic MR”, this condition has been widely attributed to infarction and ischemia in LV myocardium providing structural and contractile support for the mitral valve [4–6]. MR response to revascularization is highly variable. In approximately half of patients, MR improves with surgical revascularization (CABG), whereas in the remainder MR persists or worsens [7–11]. Limited data exist with respect to percutaneous revascularization (PCI), despite the fact that this is by far the most common means of coronary reperfusion [12]. For example, some studies have shown that MR can improve following PCI alone [13], whereas others have not [14]. Uncertainty as to which patients with MR will manifest therapeutic response to coronary revascularization limits the ability to optimize therapeutic strategies for treatment of MR.

Myocardial perfusion imaging (MPI) enables non-invasive assessment of pattern and severity of altered myocardial perfusion. Myocardial perfusion defects have been associated with presence and magnitude of MR, stemming from impaired myocardial perfusion in LV segments adjacent to the papillary muscles [15]. MPI has also been shown to predict MR response to CABG, as evidenced by greater improvement in MR among patients with more extensive viable myocardium [10]. Conventional indices of LV chamber size and function have been shown to be similar between patients with and without revascularization-induced improvement in MR [9, 10, 13, 16], highlighting the need for more accurate indices to predict MR therapeutic response.

This study examined myocardial perfusion as a predictor of MR response to PCI. The goals were two-fold; (1) to identify structural indices conferring increased likelihood of MR among patients undergoing PCI, and (2) to test whether MR response to PCI varies in relation to pattern and magnitude of impaired myocardial perfusion.

Methods

Population

The population comprised patients who underwent single photon emission computed tomography (SPECT) MPI and transthoracic echocardiography (echo) prior to percutaneous coronary intervention (PCI) between 2002 and 2013. SPECT and echo were acquired within one-week; PCI was performed within 6 months after MPI. To study ischemic MR (as opposed to MR due to other causes), patients referred for invasive angiography in the absence of abnormal perfusion, as well as those with MR due to other etiologies (prolapse, rheumatic disease, chordal rupture, endocarditis) or with prior mitral valve surgery (prosthesis, annuloplasty) were excluded.

This study was conducted with approval of the Weill Cornell Medical College institutional review board.

Imaging Protocol

SPECT—MPI was performed in accordance with a previously described protocol [17, 18]. Thallium-201 (~3 mCi) or technetium-99m sestamibi (~10 mCi) was injected intravenously; baseline (rest) perfusion images were acquired approximately 10 minutes after Tl-201, and 60 minutes after Tc-99m sestamibi. After baseline imaging, patients capable of exercise underwent treadmill testing using a Bruce protocol: Tc-99m (~30 mCi) was intravenously administered at peak stress following achievement of target heart rate response to exercise (≥85% age-predicted maximum). In patients unable to exercise or achieve adequate heart rate response, pharmacologic protocols were employed using either adenosine-based agents or dobutamine. Post-stress images were acquired ~30 minutes following exercise, and 1–2 hours following pharmacologic stress.

SPECT was performed using a dual headed scintillation camera system with a low-energy high-resolution collimator. For thallium-201 imaging, photopeaks of 70 keV and 167 keV were utilized. For technetium-99m imaging, a photopeak of 140keV was utilized. Stress images were ECG-gated for assessment of contractile function; LV chamber size and ejection fraction were quantitatively measured (Cedars-Sinai AutoQuant).

Demographic indices were categorized at time of MPI using a uniform questionnaire; results were confirmed by review of medical records. Invasive angiography was reviewed for CAD severity and PCI target. Obstructive CAD was defined using standard criteria for native coronary arteries (≥50% left main, ≥70% other major epicardial vessel) [19], or bypass grafts (≥70%).

Echocardiography—Echoes were performed by experienced sonographers using commercially available equipment (e.g. General Electric Vivid-7, Philips ie33). Images were acquired in parasternal, as well as apical 2-, 3-, and 4- chamber orientations. LV ejection fraction and chamber size were quantified using linear dimensions in parasternal views [20]. Color Doppler was used to assess MR severity based on jet area, depth, vena contracta, and directionality. Pulsed wave Doppler included assessment of MR duration, as well as pulmonary vein flow profiles.

Image Analysis

Myocardial Perfusion—MPI was interpreted by American Heart Association/American College of Cardiology (AHA/ACC) level III trained readers utilizing a standard 17-segment model [21]: High intra- and inter-observer reproducibility for MPI interpretation has been previously reported [17]. Visual assessment was confirmed by review of polar plots with comparison of segmental radiotracer intensity to computer generated normative datasets. Perfusion defect severity on a per segment basis was graded using a 5-point scoring system (0 = normal, 1 = equivocal or mildly reduced, 2 = moderately reduced, 3 = severely reduced, 4 = absent radioisotope uptake) [22]. Summed stress and rest scores were calculated by adding per-segment defect severity for all segments. Summed difference scores were

assessed as the difference between rest and stress. In accordance with prior studies, a summed stress score of ≥4 was the criterion for MPI abnormality (i.e. eligible for study inclusion) [22].

To test the relation between regional perfusion and MR, established partitions were applied to divide the LV into three equally sized (anterior, inferior, lateral) territories (Figure 1) [4]. Summed stress, rest, and difference scores in each territory were calculated as the sum of respective perfusion indices within constitutive segments. Presence of perfusion defects in one territory did not preclude classification of perfusion defects in other territories.

Mitral Regurgitation—Echoes were interpreted by experienced ACC/AHA level III trained readers in a high volume laboratory, for which methods of measurement of chamber volumes and MR have been previously reported [23]. MR severity was graded on echo using a 4-point scale, primarily determined based on distance reached from the mitral orifice by the regurgitant jet (mild [1+]; ≤0.5cm | moderate [2+]; 1.5–3.0cm | moderately-severe [3+]; 3.0–4.5cm | severe [4+]; ≥4.5cm). Additional criteria used to confirm MR severity included jet area and vena contracta ([1+]; color jet <20% LA area, vena contracta <0.3 | [2+]; color jet 20–40%, vena contracta 0.3–0.69 | [3–4+]; color jet >40%, vena contracta ≥0.7), jet density, mitral and pulmonary vein flow pattern [15, 24].

Follow-up

Echo, when performed for clinical indications, was used to assess MR and LV remodeling in accordance with baseline analytic methods. A minimum of 30 days post-PCI was the criterion for adequate follow-up; maximum follow-up was defined as 2 years post-PCI. Change in MR severity was defined as a difference of at least 1 grade vs. baseline (i.e. increased ≥ 1 grade, decreased ≤ 1 grade). Heart rate and blood pressure were obtained non-invasively at baseline (pre-PCI) and follow-up.

Statistical Methods

Comparisons of continuous variables between groups with and without MR were made using Student's t test for two group and ANOVA for multiple group comparisons; data for both are expressed as mean value±standard deviation. Categorical variables were compared using chi-square or, when fewer than 5 expected outcomes per cell, Fisher's exact test. Multivariable logistic regression analysis was performed to evaluate associations between MR and imaging parameters. Two-sided $p<0.05$ was considered indicative of statistical significance. Calculations were performed using SPSS Version 20 (IBM, Armonk, NY).

Results

Population Characteristics

The population comprised 317 patients without primary mitral valve disease who underwent SPECT MPI and echo within a one-week (0.6±2.9 day) interval. A total of 14 otherwise eligible patients were excluded based on presence of echo-evidenced primary mitral valve disease (prolapse n=8, rheumatic n=1) or prior mitral surgery (n=5).

MR was present in half (52%) of patients (76% mild, 16% moderate, 8% moderate-severe or severe). Table 1 details population characteristics, stratified by presence or absence of MR. As shown, MR was associated with clinical history of CAD, including over a 1.5 fold higher prevalence of prior MI among affected patients (p=0.01). Accordingly, adverse LV remodeling was more advanced among patients with MR, whether measured by global chamber volume on MPI or linear dimensions on echo (both p<0.001). Figure 2 stratifies MPI volumetric indices in relation to MR severity, demonstrating a stepwise increase in LV dilation and dysfunction from patients with no MR, to those with mild MR, and advanced (≥moderate) MR (both p<0.001 for trend).

Myocardial Perfusion Pattern

Table 2 compares perfusion indices in relation to presence and severity of MR. Despite the fact that all patients underwent PCI in the context of abnormal MPI, magnitude of perfusion abnormalities further stratified likelihood of MR. Differences between groups were most marked for global summed rest scores, which were 1.6-fold higher among patients with advanced MR vs. those with mild MR (p=0.004), and 2.4-fold higher vs. those without MR (p<0.001). Table 2 also shows that differences between groups were most marked with respect to inferior perfusion pattern, as evidenced by greater extent of inferior fixed perfusion deficits among patients with advanced MR vs. those with mild (p=0.004) or no (p=0.001) MR.

Multivariate regression analysis (shown in Table 3) was used to test the independent association of fixed myocardial perfusion defects with MR after controlling for corresponding clinical indices (history of MI) and adverse geometric remodeling (LV chamber dilation) as can be measured on MPI. Results demonstrated that ≥moderate MR was independently associated with extent of fixed myocardial perfusion defects on MPI, even after controlling for clinical history of MI and LV chamber volume (3A). Results were similar when echo-quantified LV chamber diameter was substituted for MPI-quantified end-diastolic volume (3B), demonstrating that the association between fixed perfusion defects and MR was independent of modality and approach used to measure LV chamber size. For both models, the relationship between MR and LV perfusion deficits showed a graded increase, such that likelihood for MR increased with larger size of LV perfusion deficit. Applied clinically, results indicate that fixed perfusion deficits involving five LV segments would be expected to yield a two-fold increase in likelihood for MR independent of modality used to measure LV chamber size.

MR Response to PCI

PCI was attempted 24±39 days following MPI. A total of 375 coronary vessels were revascularized in the study population (1.2±0.5 vessels per subject), among whom 24% of patients underwent multivessel PCI. Table 4 provides a breakdown of CAD anatomy and PCI target vessel. As shown, prevalence of multivessel CAD increased in relation to severity of MR (p=0.025). Regarding PCI, target vessels did not differ between patients with and without MR.

Follow-up via echo was available in 52% (n=86) of patients with MR prior to PCI, including 63% (n=25) of patients with advanced (≥moderate) MR. Patients with MR and follow-up were similar with respect to age, stress and rest global perfusion deficits on MPI, as well as LV chamber volume and LVEF (all p=NS) as compared to those with MR (on baseline echo) and no follow-up.

At follow-up of 1.0 ± 0.6 years after PCI, MR decreased by at least 1 grade in one third (31%) of affected patients, and increased (≥1 grade) in 12%. Of note, 26% (7/27) of patients with decreased MR manifested even greater change after PCI, including 3 patients with advanced (≥moderate) MR at baseline that near resolved (trace/none) on post-PCI echo. Hemodynamic indices at follow-up demonstrated similar heart rate in relation to change in MR following PCI (decreased MR: 69±17 bpm | unchanged: 69±17 bpm | increased: 81±23 bpm; p=0.22). Similarly, MR response status did not vary in relation to systolic (decreased: 134±13 mmHg | unchanged: 136±22 mmHg | increased: 124±22 mmHg; p=0.38) or diastolic blood pressure (decreased: 72±13 mmHg | unchanged: 67±11 mmHg | increased: 73±8 mmHg; p=0.29).

Figure 3 stratifies MR change in relation to myocardial perfusion pattern. As shown, patients with increased MR after PCI had more severe inferior perfusion defects on baseline MPI (p=0.028), whereas perfusion defects in other distributions, as well as LV chamber volumes, were similar between groups (all p=NS). Among patients with advanced (≥moderate) MR, follow-up results were similar: Inferior perfusion defects on baseline MPI were more severe among patients with increased MR after PCI (8.8±2.6) compared to those with persistent (3.8±3.5) or decreased MR (7.4±4.4) on follow-up (p=0.03). In multivariate analysis, inferior perfusion defects on baseline MPI were associated with increased MR after PCI (OR 1.2 per segment [CI 1.02–1.39], p=0.02) independent of follow-up duration (OR 0.99 [CI 0.95–1.03], p=0.63). Regarding angiographic parameters, PCI target vessel did not differ between patients with increased MR and the remainder of the cohort, as evidenced by similar rates of LM (0% vs. 3%, p= 1.0), LAD (40% vs. 50%, p= 0.74), LCX (50% vs. 36%, p= 0.49), and RCA (20% vs. 30%, p= 0.72) revascularization.

Discussion

This study demonstrates the utility of myocardial perfusion pattern for stratifying severity of ischemic MR, as well as its response to PCI. Findings, obtained in a broad patient cohort undergoing MPI prior to PCI, demonstrate ischemic MR to be strongly associated with magnitude and severity of fixed LV perfusion defects. Impact of perfusion pattern on MR was independent of LV remodeling, as evidenced by multivariate models demonstrating MR to be associated with extent of fixed perfusion defects irrespective of modality used to measure LV chamber size. Regarding regionality, inferior perfusion defects on MPI differed most markedly between patients with and without MR on echo, including differences with respect to both inferior summed rest score and number of fixed inferior segments between patients with advanced MR and those with mild or no MR (all p<0.01). Follow-up demonstrated inferior perfusion deficits to influence MR response to revascularization, as evidenced by higher inferior rest perfusion deficits among patients with increased MR after PCI.

This study is the first to examine whether pattern of impaired myocardial perfusion predicts ischemic MR response to PCI. Our results, which demonstrate MR improvement in 31% of patients, parallel findings of a recent prior study in which MR improved in 37% of patients undergoing PCI [13]. Surgical literature has similarly reported marked heterogeneity in MR improvement following surgical revascularization. Prior studies have reported MR to improve in approximately half (42–69%) of patients undergoing CABG alone [7–11]. Even when mitral annuloplasty is performed adjunctively with CABG, MR recurs in up to 33% of patients at 1 year postoperatively [25]. These data highlight the need to better identify predictors of MR response to therapy, so as to tailor particular therapeutic strategies to treat MR (i.e. revascularization and/or annuloplasty) based on underlying mechanism of MR and anticipated likelihood of therapeutic response.

Our observed association between inferior perfusion defects and MR is consistent with prior literature. Inferior wall MI has been recognized as a cause of MR due to geometric distortion within LV segments supporting the papillary muscles [26, 27]. Regional remodeling after inferior or posterior MI has also been linked to MR, due to impaired LV basal rotational mechanics [28]. Among patients with CAD, our group has reported inferior/inferolateral fixed perfusion defects to be associated with MR [15]. These associations may stem from regional differences in coronary anatomy: Angiographic studies have shown that the posteromedial papillary muscle is typically supplied by a single coronary artery, whereas the anterolateral papillary muscle is more frequently perfused by a dual supply [29]. In this context, CAD involving the posteromedial papillary muscle would be more likely to produce severe ischemia or infarction (manifest as a fixed inferior perfusion defect on SPECT), thereby more commonly resulting in compromised contractile function, altered LV geometry and MR.

Our analysis included assessment of both size and distribution of altered myocardial perfusion, so as to test the impact of perfusion pattern on ischemic MR. Prior research, which has categorized ischemia and infarction in a binary manner [13], has not demonstrated an association between altered myocardial tissue properties and MR response to PCI – highlighting the importance of distribution of myocardial injury as a determinant of both magnitude and therapeutic response of MR [4]. Consistent with our observed association between fixed perfusion defect size and worsened MR after PCI, Penicka et al. reported extent of non-viable myocardium on SPECT to predict persistent MR after CABG [10]. Regarding mechanism, adverse LV remodeling is known to provide a substrate for MR, resulting from altered papillary muscle geometry and impaired contractility of LV myocardium underlying the mitral valve. Persistent MR after CABG has been associated with adverse remodeling, as evidenced by post-operative increases in LV size and sphericity [30]. Conversely, decreased MR has been linked to decrements in LV size [31]. Myocardial viability is a key determinant of LV remodeling response to both PCI and CABG [32, 33]. Together with our findings, these data support the notion that MR response to revascularization is strongly influenced by myocardial tissue properties, irrespective of whether surgical or percutaneous strategies are used for coronary reperfusion.

It is important to recognize that this study examined patients with abnormal MPI undergoing PCI, to examine therapeutic response of ischemic MR and exclude patients in whom MR

was attributable to other causes. In this context, the association between ischemia and MR may have been blunted due to relative uniformity of the population, in that patients without ischemia/viability would not typically be treated via any means of revascularization, whereas those with more severe ischemia would be expected to undergo CABG (rather than PCI). Prior studies have demonstrated a physiologic link between ischemia and MR. Using a canine model, Kono et al demonstrated that MR could be induced with transient coronary occlusion, and relieved with reperfusion.[6] Messas et al, using a sheep model, demonstrated that inferior ischemia produced MR [5]. The importance of ischemia has also been demonstrated in population-based studies of MR. For example, among a cohort of 2,377 subjects with known or suspected CAD, our group demonstrated MR to be independently associated with magnitude of both inducible (i.e. ischemic) and fixed perfusion defects on SPECT MPI [15].

Several limitations should be noted. First, it is important to recognize that this study did not use a uniform quantitative method to measure MR, but instead applied a semi-quantitative grading system as has been used in prior research [15, 23], including a recent multicenter study of MR response to therapeutic interventions [25]. Our analytic approach did not enable assessment of absolute MR severity in relation to LV perfusion pattern. On the other hand, it is unlikely that our grading system would have disproportionately affected MR assessment in relation to a specific perfusion territory so as to bias our results. Second, dedicated viability imaging was not performed as part of the protocol, and thus it remains uncertain as to whether fixed defects in our cohort represent infarction or profoundly ischemic (i.e. hibernating) myocardium. The latter is suggested by the fact that perfusion defect size was associated with ischemic MR independent of clinically documented history of MI, suggesting the possibility that at least some fixed perfusion defects may have represented hibernating myocardium. Third, as timing of post-PCI echo was based on discretion of treating clinicians, follow-up duration was not standardized. On the other hand, our results demonstrate that inferior fixed perfusion defects were associated with increased MR independent of follow-up duration, suggesting that variability in follow-up interval did not bias study results. Regarding follow-up, an additional limitation concerns the fact that post-PCI echo was only available in 52% of patients with MR (63% with advanced [≥moderate] MR) – thus, loss to follow-up could have impacted our findings. Importantly, patients with and without follow-up were similar with respect to perfusion pattern and LV remodeling indices, consistent with the notion that our results are broadly generalizable with respect to the impact of perfusion pattern on MR response to PCI.

In conclusion, this study demonstrates that myocardial perfusion pattern not only influences severity of ischemic MR but also impacts its response to PCI. Future studies are warranted to test whether myocardial perfusion imaging can be used to guide therapeutic strategies to treat MR, towards the goal of identifying those patients in whom MR can be effectively treated with coronary revascularization alone.

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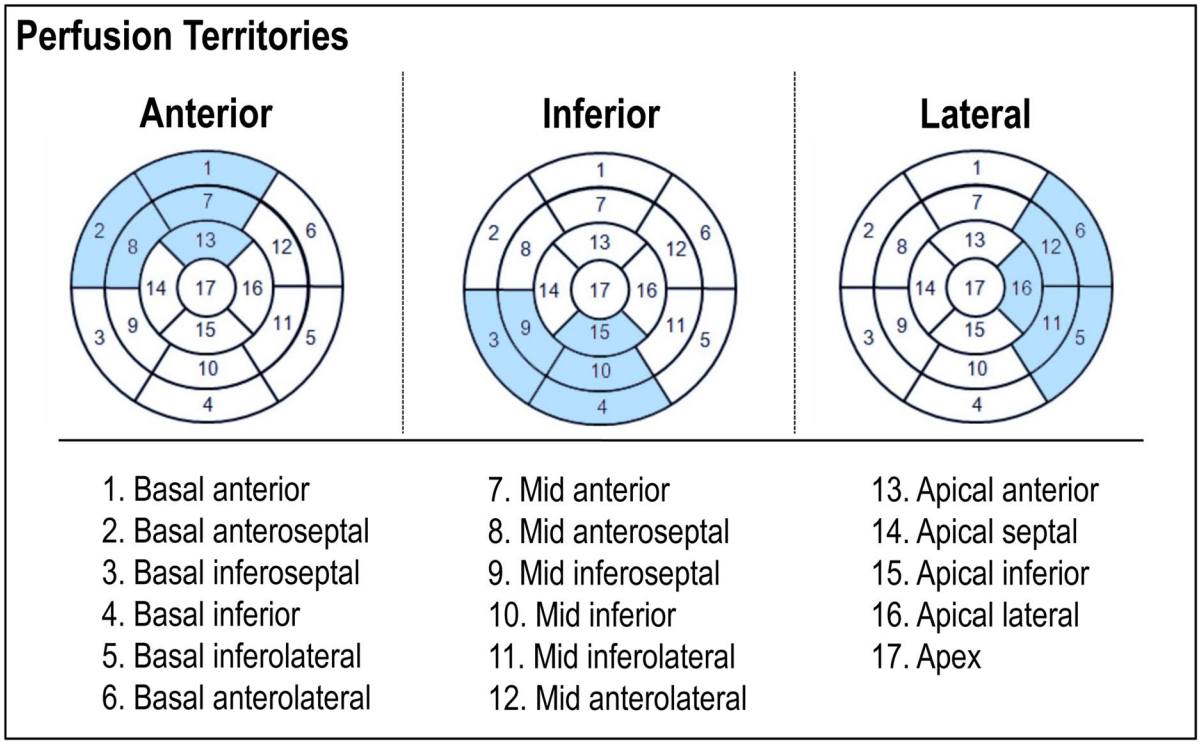

Figure 1. Myocardial Perfusion Territories

Bullseye plots illustrating regional LV perfusion territories (highlighted). Each category was comprised of five segments, such that total myocardium subtended by each was equivalent.

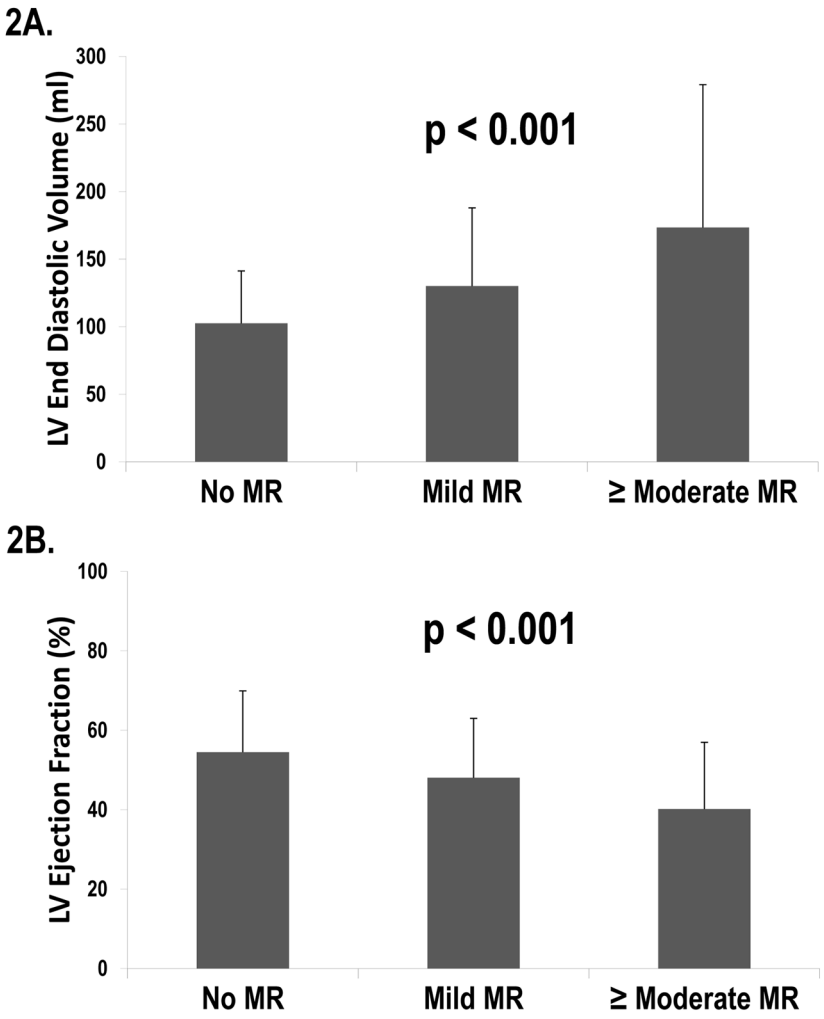

Figure 2. MPI-Quantified LV Remodeling in Relation to MR

LV end-diastolic volume (A) and post-stress ejection fraction (B) stratified in relation to presence and severity of echo-evidenced MR. As shown, both remodeling indices (mean ±SD) varied stepwise in relation to MR.

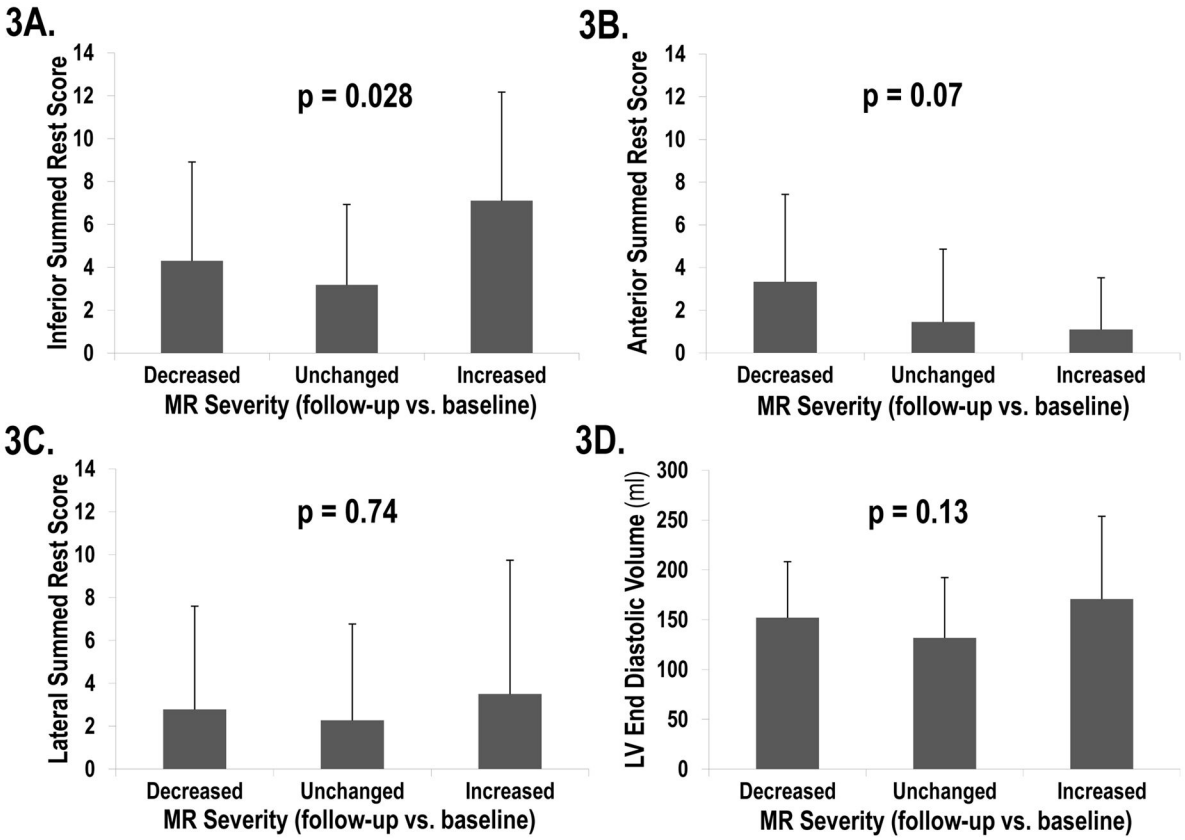

Figure 3. Myocardial Perfusion Indices in Relation to MR Response to PCI

Rest myocardial perfusion defects (A–C: summed rest scores in each respective LV territory) and (D) LV end-diastolic volume stratified in relation to change in MR following PCI. Note that severity of inferior perfusion defects on rest MPI were greater among patients with worsening MR (≥1 grade) after PCI, whereas perfusion defects in all other LV territories were similar. Data presented as mean±SD.

Table 1

Clinical and Functional Imaging Characteristics

Parameter	Overall (n=317)	Mitral Regurgitation − (n=152)	Mitral Regurgitation + (n=165)	p
Clinical				
Age (years)	68 ± 12	66 ± 12	70 ± 12	**0.002**
Male gender	70% (222)	70% (106)	70% (116)	0.91
Body Surface Area (m^2)	1.95 ± 0.50	2.00 ± 0.69	1.91 ± 0.19	0.12
Coronary artery disease risk factors				
Hypertension	75% (238)	76% (115)	75% (123)	0.82
Hypercholesterolemia	62% (195)	64% (98)	59% (97)	0.30
Diabetes mellitus	47% (149)	45% (69)	49% (80)	0.58
Tobacco use (active)	6% (20)	8% (12)	5% (8)	0.27
Family history of coronary artery disease	14% (43)	14% (21)	13% (22)	0.90
Known coronary artery disease	51% (163)	43% (65)	59% (98)	**0.003**
Prior myocardial infarction	26% (83)	20% (30)	32% (53)	**0.01**
Prior coronary revascularization				
Percutaneous coronary intervention (PCI)	15% (48)	12% (18)	18% (30)	0.12
Coronary artery bypass grafting (CABG)	25% (78)	20% (30)	29% (48)	0.053
Cardiovascular medications				
Beta-blocker	65% (207)	59% (89)	72% (117)	**0.02**
ACE inhibitor or angiotensin receptor blocker	52% (164)	49% (75)	54% (89)	0.41
HMG-CoA reductase inhibitor	60% (190)	61% (92)	59% (98)	0.84
Aspirin	67% (212)	67% (102)	67% (110)	0.93
Thienopyridine	9% (30)	9% (14)	10% (16)	0.88
Indication for stress testing				
Chest Pain	46% (147)	50% (76)	43% (71)	0.21
Dyspnea	13% (41)	15% (22)	12% (19)	0.43
Hemodynamic Indices				
Heart rate	70 ± 12	68 ± 11	72 ± 13	**0.006**
Systolic blood pressure (mmHg)	142 ± 25	141 ± 23	143 ± 26	0.54
Diastolic blood pressure (mmHg)	77 ± 13	79 ± 13	75 ± 14	**0.01**
Mean arterial pressure (mmHg)	98 ± 15	99 ± 14	97 ± 15	0.23
Imaging				
SPECT				
Stress modality				
Exercise	28% (88)	34% (52)	22% (36)	**0.01**
Adenosine/regadenoson	70% (223)	64% (97)	76% (126)	**0.02**
Dipyridamole	1% (3)	1% (1)	1% (2)	1.00
Dobutamine	1% (3)	1% (2)	1% (1)	0.61
Left ventricular function				
Post-stress ejection fraction (%)	50 ± 16	54 ± 15	46 ± 16	**<0.001**

Parameter	Overall (n=317)	Mitral Regurgitation − (n=152)	Mitral Regurgitation + (n=165)	p
Ejection fraction <50%	44% (138)	27% (41)	59% (97)	**<0.001**
LV end-diastolic volume (ml)	123 ± 63	103 ± 39	140 ± 74	**<0.001**
(ml/m^2)	63 ± 32	52 ± 18	73 ± 38	**<0.001**
Increased lung uptake	10% (32)	4% (6)	16% (26)	**<0.001**
Transient Ischemic Dilation	9% (30)	10% (15)	9% (15)	0.81
Echocardiography				
Left ventricular function/morphology				
Ejection fraction (%)	56 ± 14	60 ± 11	51 ± 15	**<0.001**
Ejection fraction <50%	28% (56)	14% (15)	42% (41)	**<0.001**
LV end-diastolic diameter (cm)	5.4 ± 0.7	5.2 ± 0.6	5.6 ± 0.7	**<0.001**
Myocardial mass (g/m^2)	111 ± 28	100 ± 27	120 ± 26	**<0.001**
Left atrial morphology				
Diameter (cm)	4.3 ± 1.9	4.0 ± 0.6	4.6 ± 2.4	**0.006**
Volume (ml/m^2)	39 ± 15	32 ± 11	44 ± 16	**<0.001**

Numbers in boldface indicate p values < 0.05

Table 2

Myocardial Perfusion Pattern

	Mitral Regurgitation - (n=152)	Mild MR (n=125)	P	Advanced (≥moderate) MR (n=40)	P (vs. mild)	P (vs. no MR)
2A. GLOBAL LV PERFUSION						
Summed Stress Score	15.5 ± 9.3	20.0 ±11.7	**0.001**	22.9 ± 11.0	0.17	**<0.001**
Summed Rest Score	5.8 ± 7.3	8.6 ± 9.4	**0.008**	13.7 ± 10.8	**0.004**	**<0.001**
Summed Difference Score	9.7 ± 6.9	11.4 ± 8.2	0.06	9.2 ± 7.1	0.12	0.65
# Ischemic Segments	4.8 ± 3.0	5.6 ± 3.1	**0.046**	5.1 ± 3.1	0.37	0.68
# Fixed Segments	1.1 ± 1.8	1.6 ± 2.3	0.09	3.2 ± 3.2	**0.005**	**<0.001**
2B. REGIONAL LV PERFUSION						
Anterior Perfusion Territory						
Summed Stress Score	3.3 ± 4.3	4.6 ± 4.6	**0.02**	4.9 ± 4.6	0.75	**0.04**
Summed Rest Score	1.0 ± 2.6	1.5 ± 3.2	0.17	2.4 ± 3.6	0.12	**0.02**
Summed Difference Score	2.3 ± 3.1	3.2 ± 3.4	**0.04**	2.5 ± 2.5	0.24	0.78
# Ischemic Segments	1.3 ± 1.5	1.7 ± 1.5	**0.01**	1.5 ± 1.6	0.47	0.33
# Fixed Segments	0.2 ± 0.6	0.3 ± 0.9	0.36	0.6 ± 1.0	0.13	**0.04**
Inferior Perfusion Territory						
Summed Stress Score	5.3 ± 4.3	6.1 ± 4.7	0.18	8.3 ± 4.3	**0.01**	**<0.001**
Summed Rest Score	2.7 ± 3.4	3.2 ± 3.9	0.19	5.7 ± 4.4	**0.001**	**<0.001**
Summed Difference Score	2.7 ± 3.1	2.8 ± 3.4	0.71	2.6 ± 3.3	0.71	0.89
# Ischemic Segments	1.5 ± 1.5	1.6 ± 1.6	0.72	1.6 ± 1.9	0.97	0.84
# Fixed Segments	0.7 ± 1.1	0.7 ± 1.3	0.56	1.6 ± 1.6	**0.004**	**0.001**
Lateral Perfusion Territory						
Summed Stress Score	4.0 ± 5.0	5.6 ± 6.1	**0.03**	5.5 ± 5.6	0.93	0.11
Summed Rest Score	1.2 ± 3.1	2.1 ± 4.3	**0.03**	2.9 ± 3.9	0.34	**0.01**
Summed Difference Score	2.9 ± 3.7	3.4 ± 4.0	0.24	2.6 ± 3.5	0.25	0.68
# Ischemic Segments	1.6 ± 1.9	1.8 ± 1.8	0.36	1.5 ± 1.8	0.33	0.75
# Fixed Segments	0.2 ± 0.7	0.4 ± 1.0	0.08	0.7 ± 1.1	0.09	**0.01**

* Perfusion territories are defined in Figure 1.

Table 3

Multivariate Models for Advanced (≥moderate) MR

A.

	Univariate Regression		Multivariate Regression *Model chi-square = 27.69, p < 0.001*	
Variable	**Odds Ratio (95% Confidence Interval)**	**P**	**Odds Ratio (95% Confidence Interval)**	**P**
Fixed Perfusion Defect Size (per segment)	1.31 (1.16 – 1.47)	**<0.001**	1.16 (1.002 – 1.34)	**0.046**
LV End-Diastolic Volume (per 10 ml)	1.13 (1.07 – 1.18)	**<0.001**	1.10 (1.04 – 1.17)	**0.002**
Myocardial Infarction (clinically documented)	1.93 (0.97 – 3.85)	0.06	0.90 (0.40 – 2.04)	0.79

B.

	Univariate Regression		Multivariate Regression *Model chi-square = 22.80, p < 0.001*	
Variable	**Odds Ratio (95% Confidence Interval)**	**P**	**Odds Ratio (95% Confidence Interval)**	**P**
Fixed Perfusion Defect Size (per segment)	1.31 (1.16 – 1.47)	**<0.001**	1.28 (1.10 – 1.48)	**0.001**
LV Internal Diastolic Diameter (cm)*	2.30 (1.38 – 3.83)	**0.001**	1.49 (0.85 – 2.62)	0.17
Myocardial Infarction (clinically documented)	1.93 (0.97 – 3.85)	0.06	1.12 (0.51 – 2.49)	0.78

* measured via transthoracic echo

Table 4

Anatomic Distribution of Obstructive CAD

	MR - (n=152)	Mild MR (n=125)	Advanced (≥moderate) MR (n=40)	P
4A. Coronary Obstruction				
Left Main (LM)	5% (8)	7% (9)	18% (7)	**0.03**
Left Anterior Descending (LAD)	74% (113)	86% (108)	78% (31)	**0.04**
Right Coronary (RCA)	59% (90)	69% (86)	78% (31)	0.06
Left Circumflex (LCX)	57% (87)	64% (80)	68% (27)	0.35
Multivessel Obstructive CAD	64% (98)	78% (97)	80% (32)	**0.025**
4B. PCI Target Vessel				
Left Main (LM)	2% (3)	3% (4)	5% (2)	0.56
Left Anterior Descending (LAD)	48% (73)	53% (66)	55% (22)	0.62
Right Coronary (RCA)	35% (53)	28% (35)	35% (14)	0.44
Left Circumflex (LCX)	30% (45)	37% (46)	28% (12)	0.35

* Obstructive CAD defined using standard criteria for native coronary arteries (≥50% left main, ≥70% other major epicardial vessel) [19], or bypass grafts (≥70%).