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## Infarction, ischemia and function in patients with ischemic mitral regurgitation: Abnormal strain overestimates non-viable myocardium

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### Abstract

**Objective**—Therapy for moderate ischemic mitral regurgitation (IMR) remains unclear.

Determination of myocardial viability, a necessary pre-requisite for an improvement in regional contractility, is a likely key factor in determining response to revascularization alone. Myocardial strain has been proposed as a viability measure but has not been compared to late gadolinium enhancement (LGE) cardiac (c)MRI. We hypothesized that abnormal strain overestimates non-viable LV segments measured using LGE and that ischemia and mechanical tethering by adjacent transmural myocardial infarction (TMI) also decreases strain in viable segments.

**Methods**—Sixteen patients with mild IMR and seven healthy volunteers underwent cMRI with non-invasive tags (CSPAMM), LGE and stress perfusion. CSPAMM images were post-processed with HARP and circumferential and longitudinal strains were calculated. Viability was defined as the absence of TMI on LGE (hyperenhancement >50% of wall thickness). The borderzone was defined as any segment bordering TMI. Abnormal strain thresholds ( $\pm 1-2.5$  SD from normal mean) were compared to TMI, ischemia and borderzone.

**Results**—7.4% of LV segments had TMI on LGE while >14.5% of LV segments were non-viable by strain thresholds ( $p < 0.005$ ). In viable segments, ischemia impaired longitudinal strain (least perfused 1/3 of LV segments  $-0.18 \pm 0.08$  vs. most perfused  $-0.22 \pm 0.1$   $p = 0.01$ ) and circumferential strain ( $-0.12 \pm 0.1$  vs  $-0.16 \pm 0.08$   $p < 0.05$ ). In addition, infarct proximity impaired longitudinal strain ( $-0.16 \pm 0.11$  borderzone vs  $-0.18 \pm 0.09$  remote  $p = 0.05$ ).

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**Conclusions**—Impaired LV strain overestimates non-viable myocardium when compared to TMI on LGE. Ischemia and infarct proximity also decrease strain in viable segments.

## Introduction

Therapy for moderate ischemic mitral regurgitation (IMR) remains unclear. Forty-seven to 68% of patients with moderate IMR that are treated with coronary bypass alone have less than moderate IMR one to two years after revascularization [1, 2]. An important clinical target, therefore, is development of a predictive model that can accurately triage patients to revascularization or revascularization plus mitral repair based on preoperative characteristics.

It is generally accepted that the primary cause of IMR is leaflet restriction due to lateral displacement of the papillary muscle [3] a concept that is supported by the ability of operations that reposition the papillary muscle to reduce or abolish IMR [4, 5]. On the other hand, regional left ventricular (LV) contractile function is also a factor. For instance, dobutamine is known to reduce IMR in 60% of patients with reduced global LV function [6]. In conjunction with the response of moderate IMR to revascularization alone [1, 2], this suggests that improvement of regional contractility plays a significant role.

Myocardial viability is a necessary but not sufficient condition for recovery of contractile function with revascularization. For instance, the amount of interstitial fibrosis [7] determines whether hibernating myocardium will regain contractility with revascularization. However, without viability, there is no possibility of contractile recovery or reverse remodeling.

Cardiac (c)MRI provides several methods of viability assessment [8]. Late gadolinium contrast enhancement (LGE) has been correlated with the extent of myocardial necrosis and scar in tissue samples [9]. Viability measured by LGE has also been clinically linked to the likelihood of functional recovery after myocardial infarction [9, 10].

Mollema et al previously found that global LV strain predicts recovery of function after acute MI [11] and more recently, Lancaster et al proposed abnormal end-systolic strain, measured with cMRI with tags, as a new measure of viability [12]. Cupps et al previously determined that strain  $>1.5$  standard deviations (SD) from the mean value in normal patients was correlated with non-viable regions detected on PET and SPECT [13]. However, this strain method has not been validated in patients with IMR, and to date there have been no direct comparisons of strain-based viability studies with transmural MI on LGE.

To determine whether abnormal systolic strain is a measure of myocardial viability in patients with IMR, we compared end-systolic circumferential and longitudinal strain measured using cMRI with tags to myocardial viability determined by LGE MRI. We tested the hypotheses that abnormal strain over-estimates the amount of non-viable myocardium and that ischemia and infarct proximity (borderzone) contribute to abnormal strain in viable LV segments.

## Patients and Methods

Patients were prospectively enrolled in a protocol examining IMR-associated remodeling. Imaging was performed at Weill Cornell Medical College (New York, NY). The Cornell Institutional Review Board approved this study, and written informed consent was obtained at time of enrollment.

### Study population

Eligible patients had documented history of MR ( mild) and were being considered for invasive coronary angiography because of known obstructive CAD or abnormal stress test. Patients with primary MR, prior mitral valve replacement, or contraindications to MRI or gadolinium (glomerular filtration rate < 30 ml/min/1.73 m<sup>2</sup>) were excluded. Echocardiography was performed within 3 days of MRI to confirm MR severity, which was graded on a 5-point scale according to consensus criteria, based on aggregate data yielded by vena contracta, volumetric indices, jet depth, and mitral and pulmonary vein flow pattern [14]. Control imaging was performed in asymptomatic volunteers without cardiovascular risk factors.

### Magnetic Resonance Imaging

MRI was performed using 3.0 Tesla scanners (General Electric, Waukesha, WI). Sequences included 1) Cine-MRI with steady-state free precession to assess cardiac structure/function, 2), Gadolinium-enhanced first pass regadenoson-induced stress perfusion (4–5 equidistant LV short-axis images) to assess LV ischemia, 3) Delayed-enhancement inversion recovery MRI for LGE, 10–30 minutes after administration of gadolinium (0.2 mmol/kg) using a segmented inversion recovery sequence, with inversion time tailored to null viable myocardium, to assess infarction, and (4) non-invasive tags using the CSPAMM imaging sequence in contiguous LV short and long axis slices (8 mm tag spacing, 10 mm slice thickness, no gap) for myocardial deformation and strain (Figures 1 and 2). The CSPAMM sequence was designed to prevent tag fading at end-systole [15].

### Image analysis

Each LV was divided into 17 AHA segments. The LV apex (segment 17), which is difficult to define on short-axis images, was excluded [16].

LV infarct size on LGE was graded based on transmural extent of hyperenhancement on a 0–4 point scale, where 0 = absent, 1=1–25%, 2=26–50%, 3=51–75%, 4=76–100% [9]. The infarct borderzone was defined as any LV segment directly bordering a segment with transmural infarction on LGE.

Semi-quantitative perfusion was measured using the upslope ratio technique, where the ratio = maximum upslope of the signal intensity curve for a myocardial segment/maximum upslope of signal intensity for the LV cavity, using commercially available image processing software (CAAS-MRV, the Netherlands) [17]. Perfusion in segments without TMI was stratified into three groups based on semi-quantitative perfusion results: Most perfused

(tissue/LV cavity upslope ratio >0.4); mid-perfusion (ratio 0.4–0.33); and least perfused (0.1–0.32).

### Strain calculation

Three-dimensional end-systolic circumferential and longitudinal strains were calculated from the CSPAMM images with the HARmonic Phase (HARP) method developed by Osman et al. [18] (Appendix). HARP has been validated in synthetic images [19] and in a gel phantom under shear [20]. Normal strain mean and SD by segment were determined from volunteer images.

### Viability assessment

Viability was defined as the absence of TMI on LGE (hyperenhancement >50% of wall thickness).

Strain-based cutoffs for viability assessment were set sequentially at 1, 1.5, 2, and 2.5 SD from the normal mean. Sensitivity, specificity, and positive and negative predictive values of each strain cutoff metric as a measure of viability were calculated.

### Statistical methods

Data is shown as mean  $\pm$  SD. A p value  $\leq$  0.05 was considered statistically significant.

The effects of TMI, ischemia, borderzone, IMR grade and LV end diastolic dimension on circumferential and longitudinal strain were determined using mixed-model regression analysis (Proc Mixed, SAS). McNemar's test was used to compare the overall similarity of LGE with strain-based viability methods. [21].

## Results

Sixteen patients with IMR and seven normal volunteers underwent cardiac MRI and a total of 368 LV sectors (256 IMR and 112 volunteer controls) were analyzed.

### Patient characteristics

IMR patient characteristics are seen in Table 1. Briefly, in the IMR patient group, average MR severity was  $2.38 \pm 0.96$ , with regurgitant fraction of  $40.6 \pm 15.1\%$ . Average LV end-diastolic diameter was  $5.87 \pm 0.47$  and end-systolic volume index was  $64.81 \pm 31.13$ .

### LGE measurement of MI

77 of 256 myocardial segments exhibited hyperenhancement on LGE and of those, 19 (7.4%) were transmural. TMI was most commonly located in basal and mid inferolateral regions (Figure 3A; Sectors 5 and 11). Conversely, the borderzone was most common in inferior and anterolateral regions (Figure 3B; Sectors 4, 6, 10, 12, and 15).

### Myocardial stress perfusion

Figure 3C shows the spatial distribution of stress perfusion. Least perfused segments were most occurred in inferior and inferolateral regions (Sectors 4, 5, 10, 11, 15).

### End-systolic strain

Table 2 shows strain by segment for study patients with IMR and normal volunteers. Average end-systolic longitudinal and circumferential strains in segments without infarction were  $-0.20 \pm 0.11$  and  $-0.14 \pm 0.08$  respectively, compared to  $-0.12 \pm 0.08$  and  $-0.09 \pm 0.15$  in segments with transmural infarction,  $p < .001$  (longitudinal) and  $p = .001$  (circumferential).

### End-systolic strain and viability

Figure 4A illustrates the relationship between strain and transmural extent of infarction.

Strain from normal volunteers was used to calculate viability thresholds of 1, 1.5, 2, and 2.5 SD from the normal mean. The percent of IMR patient segments beyond each of these viability thresholds is shown in Figure 4B. With the most restrictive cutoff, strain 1 SD from normal, 47.7% of segments were classified as non-viable based on longitudinal strain, and 40.6% based on circumferential strain. Using the most permissive cutoff of strain 2.5 SD from normal, 21.1% of segments were non-viable by longitudinal strain, and 14.5% non-viable by circumferential strain. Each strain threshold classified significantly more segments as non-viable than the LGE reference standard (all  $p < .005$ ). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of strain thresholds are shown in Table 3.

### Ischemia effect on strain

Figure 5A shows the progressive impairment in strain with worsening tissue perfusion; segments in the least perfused group had average longitudinal and circumferential strains of  $-0.18 \pm 0.08$  and  $-0.12 \pm 0.10$ , compared to  $-0.22 \pm 0.10$  and  $-0.16 \pm 0.08$  in the most perfused segments,  $p = .05$  (longitudinal) and  $.3$  (circumferential).

### Effect of infarct proximity on strain

Figure 5B shows the progressive strain impairment with proximity to transmural infarct. Longitudinal and circumferential strain in remote regions were  $-0.18 \pm 0.09$  and  $-0.14 \pm 0.08$ ; in the borderzone  $-0.16 \pm 0.11$  and  $-0.13 \pm 0.12$ , and in the infarct regions  $-0.12 \pm 0.12$  and  $-0.09 \pm 0.09$ . Differences between the infarct and remote zones were statistically significant ( $p < .001$  longitudinal,  $p = .002$  circumferential); differences between the infarct and the borderzone were also significant ( $p = .01$  longitudinal,  $.002$  circumferential); longitudinal strain was significantly different between the borderzone and remote zone ( $p = .05$ ).

### Effect of MR grade on strain

There was no significant effect of MR grade on strain.

### Comparison to normal volunteers

Normal segments in the ischemic MR patient population were defined as those with no infarct, in the highest 1/3 of perfusion, and remote from infarct regions. Average longitudinal and circumferential strain in these normal segments was  $-0.21 \pm 0.08$  and  $-0.15 \pm 0.09$  respectively, compared to  $-0.24 \pm 0.05$  and  $-0.18 \pm 0.05$  in normal patients ( $p = .2$  longitudinal,  $.03$  circumferential).

## Comment

The principle finding of this study is that in patients with IMR end-systolic strain significantly overestimates the number of non-viable myocardial segments. This effect can be partly explained by the fact that ischemia and proximity to transmural infarction impair strain in viable regions. Furthermore, strain in “normal” myocardial regions in patients with IMR is significantly impaired relative to myocardial strain in patients without IMR.

### Measures of myocardial viability

Measures of viability that correlate with functional improvement after revascularization include LGE, PET, SPECT, and dobutamine-stress MRI or echocardiography [22]. One major advantage of LGE over other modalities is the ability to detect the transmural extent of non-viable myocardium in a single segment, allowing viability to be expressed as a continuous, rather than binary variable [8]. This has been verified by histologic studies that found that LGE correlates directly with transmural extent of infarct [10].

In addition, transmural infarct extent on LGE predicts contractile recovery after revascularization. Prior studies demonstrate that LV segments with 50–75% transmural infarct have a 10% chance of functional recovery, which reduces to zero for >75% infarct transmural extent [9, 23, 24]. We can apply this data to our findings. The group labeled “transmural infarct” consists of 11 segments with 50–75% infarct and 8 with >75%. Therefore, one segment would be expected to recover function, and LGE is over-estimating non-viability by ~5%. In contrast, the most conservative strain threshold classified 37 segments as non-viable; accounting for the 18 segments described above which are not expected to recover, this threshold over-estimates non-viability by 51%.

### Strain thresholds for viability

Moazami and colleagues found that myocardial strain >1.5 SD above the normal mean correlated with SPECT or PET predictions of viability 90% of the time [25]. However, none of the strain thresholds tested in the current study satisfactorily determined viability. For instance, a threshold of 1 SD had moderate sensitivity (68.8 and 84.2% for longitudinal and circumferential strain respectively) but poor specificity. If the threshold is increased to 2.5 SD, specificity increased to 81.0 and 88.6% for longitudinal and circumferential strain respectively but sensitivity decreased significantly.

There are 2 mechanisms whereby myocardium without necrosis might exhibit impaired end-systolic strain. First, in areas of healthy tissue bordering regions of infarct (the MI borderzone), high mechanical load and abnormal contractile protein function decrease the contractility of viable myocardium [26, 27]. Second, after prolonged ischemia, hibernating myocardium may be thinned and hypo- or akinetic, but undergo reverse remodeling and recovery of normal contractile function after revascularization [28]. Aside from infarct proximity and ischemia, other factors also play a role in the abnormal strain seen in viable regions. Strain in our IMR patient population is globally impaired, such that even “normal” IMR segments, that are not infarcted, not ischemic, and remote from infarcted regions, have significantly impaired strain relative to normal volunteers.

## Viability for triage of patients with IMR

Viability is likely a key factor in the construction of a predictive model that would triage patients with IMR. On the other hand, recent prospective trials (STICH, HEART, PARR-2) have called into question the idea of viability as a predictor of improved outcomes in ischemic heart failure [29–31]. Each of these trials has specific issues: HEART was underpowered to detect improvement; PARR-2 did not demonstrate significant benefit in their overall study population, but subgroup analysis showed benefit in the patients whose management was actually guided by the PET results; STICH viewed myocardial viability as a binary variable, and classified the overall LV as viable if it had >55% viable segments, rather than analyzing segments for viability independently. None of these trials focused specifically on IMR, where improvement in LV function and reverse remodeling determine response to treatment.

## Limitations

This study included a small sample of patients with mild to moderate IMR. Patients with severe MR often struggle to tolerate prolonged breath-holds and supine positioning during MRI acquisition. We are actively improving our imaging protocols to decrease the time required for strain imaging, anticipating an increase in the number of patients with severe MR who can tolerate the full imaging sequence.

Follow-up imaging is not available for the majority of the patients included in this study, precluding us from measuring degree of functional recovery after revascularization.

## Conclusions

Strain-based viability metrics overestimate the number of non-viable myocardial segments when compared to LGE MRI. This effect can be partly explained by the fact that ischemia and proximity to transmural infarction impair strain in viable regions. Patients with IMR also have significant strain impairment in non-ischemic, non-infarcted and remote regions of the LV. Using strain as a viability measure in these patients will exclude large numbers of myocardial segments with the potential for full functional recovery after revascularization.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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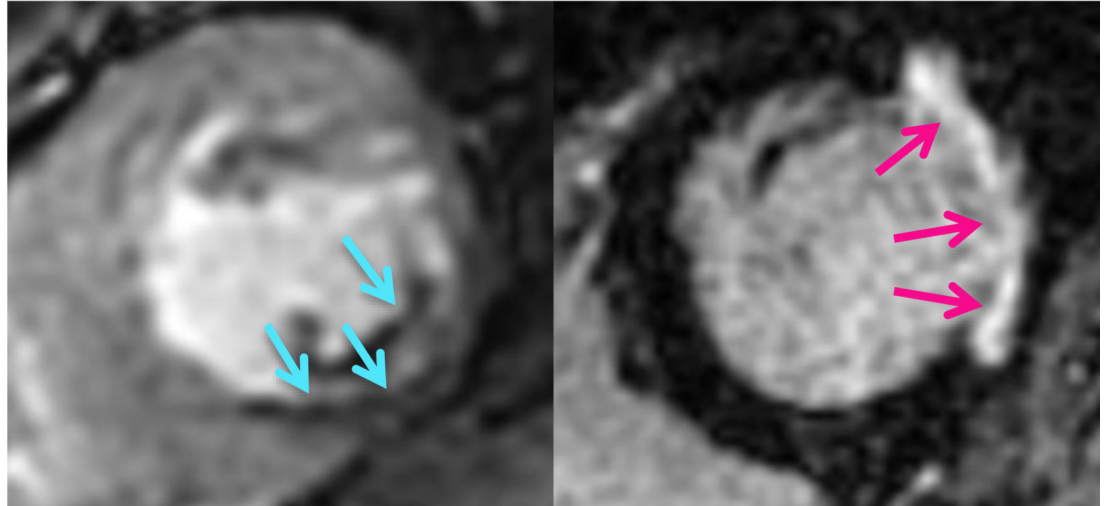
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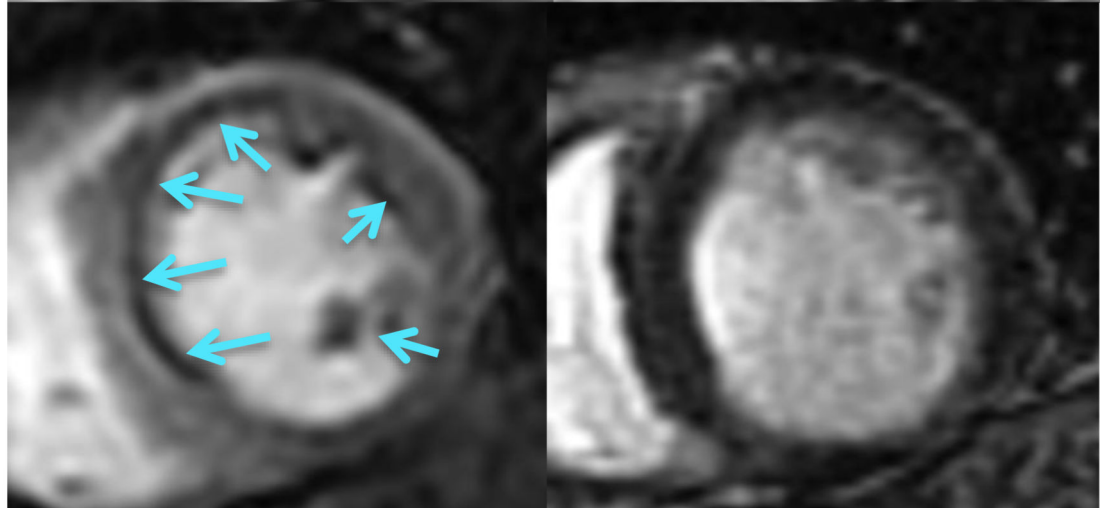
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# Perfusion      Late Gadolinium Enhancement

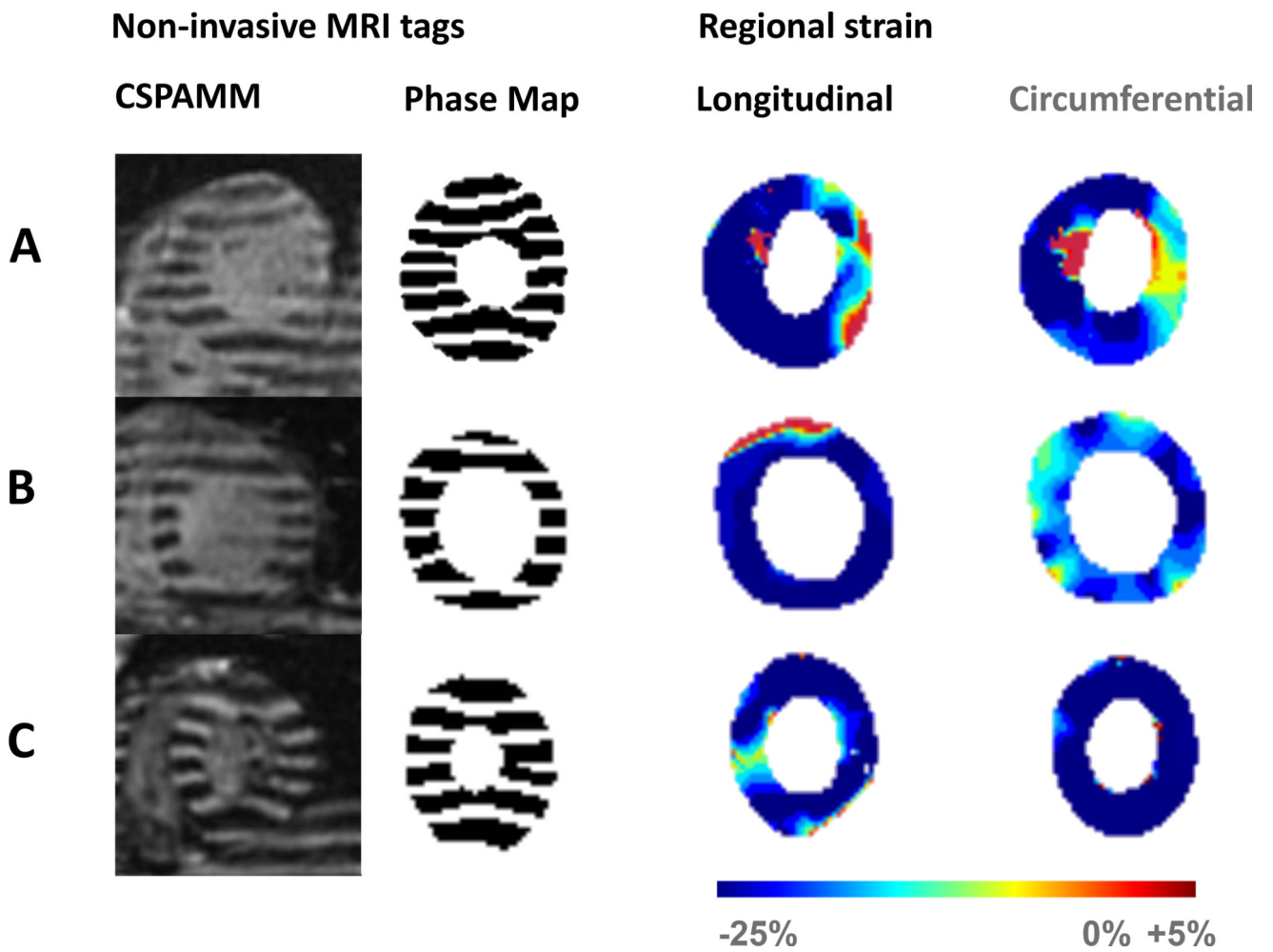
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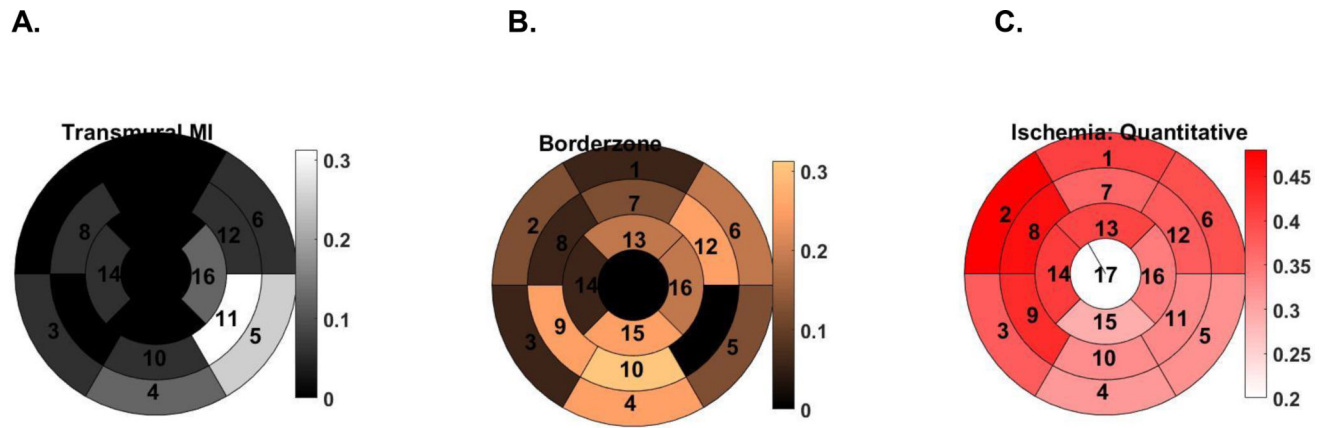
**B**



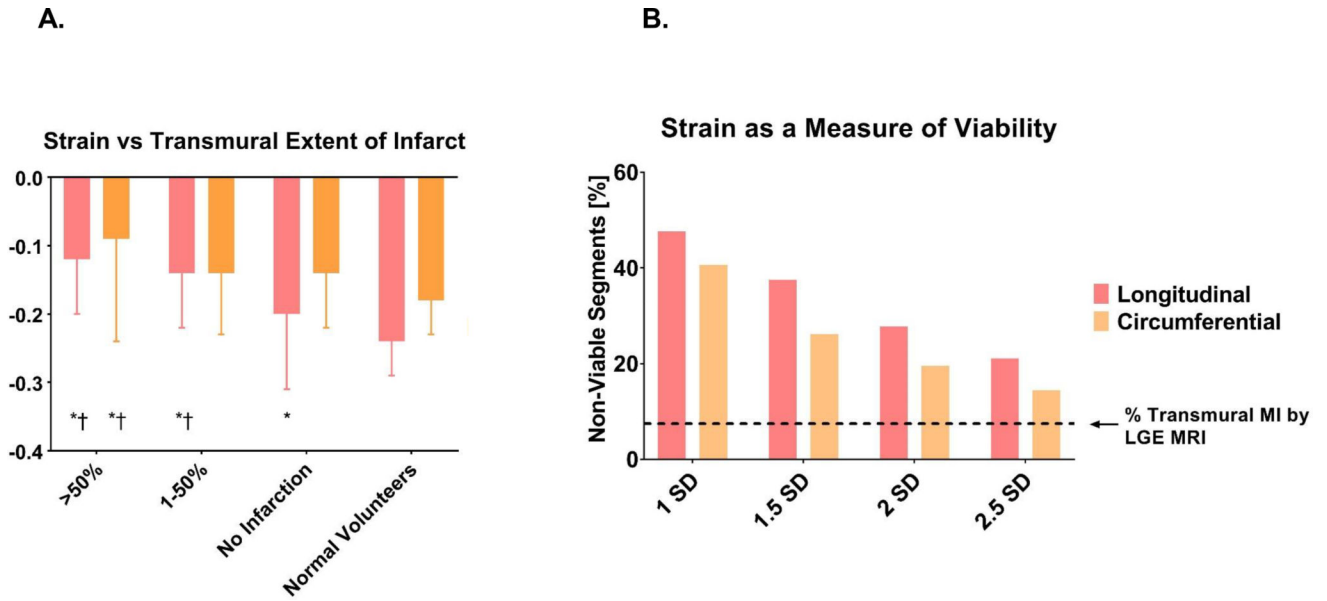
**Figure 1.** Stress perfusion and late gadolinium enhancement (LGE/infarct) MRI sequence in a patient with IMR, stress ischemia, and a transmural infarct (**A**) and a patient with IMR, stress ischemia, and no infarct (**B**).



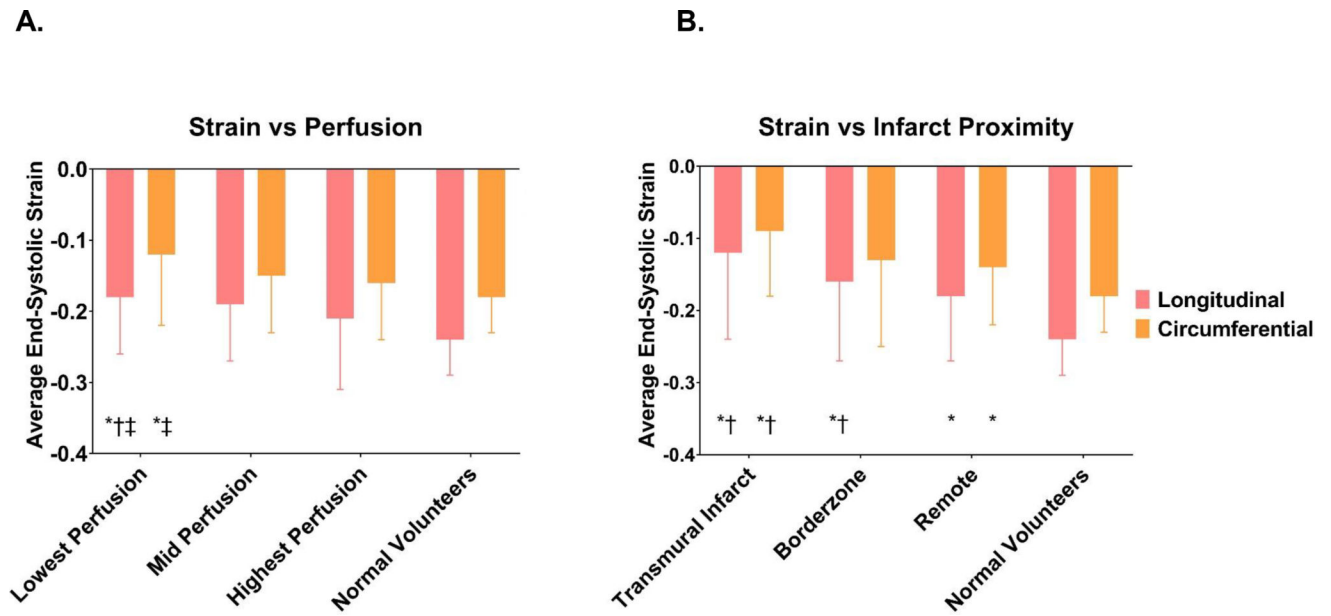
**Figure 2.** Tagged strain images at end-systole for patient **A** and **B** described in figure **1A**, as well as a normal volunteer (**C**), with corresponding phase maps and end-systolic longitudinal and circumferential strain maps.



**Figure 3.** AHA 17 sector plots showing the proportion of patients that had transmural MI (**A**), borderzone designation (**B**) and ischemia (**C**) by sector.



**Figure 4.** Relationship between strain and transmural extent of myocardial infarction (**A**) and strain as an index of viability (**B**). \* =  $p < 0.05$  relative to normal volunteers. † =  $p < 0.05$  relative to segments with no infarct for Panel A. Panel B shows the percent of 256 total segments classified as non-viable using strain thresholds from 1–2.5 standard deviations (**SD**) from the mean in normal patients. Dashed line shows the % transmural MI by LGE MRI. \* =  $p < 0.05$  relative to delayed enhancement, by McNemar’s test.



**Figure 5.**

The effect of perfusion (**A**) and infarct proximity (**B**) on end-systolic strain. \* =  $p < 0.05$  relative to normal volunteers; † =  $p < 0.05$  relative to highest perfusion group. ‡ =  $p < 0.05$  relative to mid perfusion group for Panel A. \* =  $p < 0.05$  relative to normal volunteers; † =  $p < 0.05$  relative to remote segments for Panel B.

**Table 1**

## Demographic and Clinical Characteristics of the Study Population

Age (years)	71 ± 10
Gender	81% Male, 19% Female
MR Severity (0–5 scale)	2.38 ± 0.96
Regurgitant Fraction (%)	40.64 ± 15.14
LV End-diastolic Dimension (cm)	5.87 ± 0.47
LV End-diastolic Volume Index (ml/ m <sup>2</sup> )	105.16 ± 30.63
LV End-systolic Volume Index (ml/ m <sup>2</sup> )	64.81 ± 31.13
LV Ejection Fraction (%)	40.87 ± 13.43
MI on Current Imaging:	15/16 (94%)
Lateral Wall	11/16 (69%)
Inferior Wall	11/16 (69%)
Anterior Wall	9/16 (56%)
NYHA Functional Class	1.6 ± 0.8
History of MI	10/16 (63%)
Previous PCI	11/16 (69%)
Previous CABG	5/16 (31%)
Diabetes	9/16 (56%)
Tobacco Use	9/16 (56%)
HTN	13/16 (81%)



**Table 2**  
Average End-Systolic Strain by AHA Segment in Normal Volunteers and patients with IMR.

AHA Segment	Circumferential Strain			Longitudinal Strain		
	Normal Volunteer	IMR	p	Normal Volunteer	IMR	p
1	-14±.08	-10±.14	NS	-24±.06	-18±.07	NS
2	-15±.05	-10±.07	NS	-22±.04	-19±.06	NS
3	-15±.05	-15±.05	NS	-25±.05	-15±.12	.02
4	-18±.04	-12±.07	NS	-22±.06	-17±.12	NS
5	-21±.03	-15±.09	NS	-24±.06	-17±.13	NS
6	-20±.06	-17±.06	NS	-27±.07	-20±.06	NS
7	-19±.05	-14±.04	NS	-23±.04	-16±.11	NS
8	-17±.05	-13±.07	NS	-23±.04	-20±.08	NS
9	-17±.06	-15±.05	NS	-24±.04	-20±.09	NS
10	-18±.03	-13±.11	0.03	-21±.09	-18±.14	NS
11	-21±.04	-13±.10	0.03	-23±.04	-16±.11	0.05
12	-22±.05	-19±.04	NS	-26±.04	-17±.07	.03
13	-17±.07	-16±.05	NS	-21±.04	-17±.12	NS
14	-18±.04	-14±.06	NS	-25±.04	-22±.06	NS
15	-17±.05	-05±.18	0.01	-21±.05	-17±.08	NS
16	-22±.06	-19±.05	NS	-23±.04	-13±.14	0.01
Average	-18±.05	-14±.09	<0.001	-24±.05	-18±.10	<0.001

Diagnostic performance of longitudinal and circumferential strain as a measure of viability, using transmural infarction on LGE as the reference standard. Non-viable segments are defined as segments with  $|\text{strain}| < |\text{mean normal strain} - (\text{standard deviation} * \text{threshold})|$ .

**Table 3**

Longitudinal Strain Threshold	Sensitivity	Specificity	PPV	NPV	Accuracy
1	68.4% (13/19)	54% (128/237)	10.7% (13/122)	95.5% (128/134)	55.1% (141/256)
1.5	57.9% (11/19)	64.1% (152/237)	11.5% (11/96)	95% (152/160)	63.7% (163/256)
2	52.6% (10/19)	74.3% (176/237)	14.1% (10/71)	95.1% (176/185)	72.7% (186/256)
2.5	47.4% (9/19)	81.0% (192/237)	16.7% (9/54)	95.1% (192/202)	78.5% (201/256)
Circumferential Strain Threshold	Sensitivity	Specificity	PPV	NPV	Accuracy
1	84.2% (16/19)	62.9% (149/237)	15.4% (16/104)	98% (149/152)	64.5% (165/256)
1.5	78.9% (15/19)	78.1% (185/237)	22.4% (15/67)	97.9% (185/189)	78.1% (200/256)
2	68.4% (13/19)	84.4% (200/237)	26% (13/50)	97.1% (200/206)	83.2% (213/256)
2.5	52.6% (10/19)	88.6% (210/237)	27% (10/37)	95.9% (210/219)	85.9% (220/256)