# An Area-Based Imaging Biomarker for the Characterization of Coronary Artery Stenosis with Blood Oxygen-Sensitive MRI

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**Introduction:** BOLD MRI may be used for detecting myocardial oxygenation changes secondary to coronary artery stenosis (1-3). Under pharmacological stress, the myocardial bed supplied by the stenotic coronary artery appears hypointense relative to healthy regions in BOLD images. Manual windowing (to visualize signal changes) and segmentation according to the American Heart Association's (AHA) recommendation are often used to characterize the BOLD effect. However, current approaches for analyzing BOLD changes are suboptimal for detecting critical stenosis (reduction in perfusion reserve below 2:1). The purpose of this study is to test the hypothesis that, **ARREAS** (***A***rea-based bioma***R***ker for cha***R***act***E***rizing coron***A***ry ***S***tenosis), an area-based statistical approach relying on the differences between rest and stress images, can characterize BOLD changes in end-systole and end-diastole with exquisite sensitivity and specificity. This hypothesis was tested in a canine model.

**Methods:** Imaging Studies: 2D cine SSFP-based BOLD images were acquired in 9 dogs under rest, and adenosine stress with and without LCX stenosis (of varying grades, controlled by surgically implanted hydraulic occluder) in a 1.5T scanner. Scan parameters: spatial resolution=1.2x1.2x6mm$^3$; flip-angle=90$^o$; and TR/TE=6.2/3.1ms. Microsphere analysis was used to measure true perfusion. First-pass perfusion (FPP) and late-enhancement (LE) scans were performed to visually confirm perfusion deficits and absence of infarction. Following imaging studies and euthanization, the heart was sectioned into short-axis rings and the myocardial tissue was processed (in a segmental fashion) to ascertain perfusion. Microsphere flow within each AHA segment was summed to obtain total flow per slice (4). *Microsphere Flow Ratio* (MFR), defined as the ratio of flow between stress and rest was computed. Image Processing: End-systolic (ES) and end-diastolic (ED) images were identified automatically (5) and myocardial borders were traced. Myocardial pixel intensities from rest images were fitted to location-scaled Student's *t*-distribution to estimate the location ($\mu$) and scale ($\sigma$) parameters. *Affected-Fraction* (AF), defined as the ratio of the area of the largest contiguous hypointense region (pixel intensity below $\mu-\sigma$) divided by the total area of the myocardium, was computed for both stress ($AF_{STRESS}$) and rest ($AF_{REST}$) cases. *Ischemic-Extent* (IE), was defined/computed as $IE = AF_{STRESS}/AF_{REST}$. For comparison, mean signal intensities of AHA segments corresponding to the LCX territory were normalized by the mean intensity of the entire myocardium to obtain $I_{REST}$ and $I_{STRESS}$. *Segment-Intensity-Response* (SIR), was defined/computed as $SIR = I_{STRESS} / I_{REST}$. For visualization purposes myocardial pixels with intensities below $\mu-\sigma$ *are* color-mapped to red and yellow colors corresponding to the pixel intensity values of 0 and $\mu-\sigma$, respectively. Statistical analysis: IE and SIR derived from ES and ED images were each regressed with MFR. Receiver-Operating-Characteristic (ROC) analysis was used to examine the diagnostic capacities of IE and SIR metrics to detect critical stenosis at ES and ED on the basis that a perfusion ratio between stress and rest of 2:1 (or below, that is a MFR ≤2) leads to a significant perfusion anomaly (6).

**Results:** Fig. 1 shows representative FPP, ARREAS-processed BOLD and LE images from a severe stenosis study. Note the close correspondence between the FPP and the BOLD image processed using ARREAS under similar physiological conditions. Fig. 2 illustrates scatter plots and fits between IE or SIR and MFR from 26 studies. IE values derived from ES BOLD images showed a stronger correlation to an exponential ($R^2$= 0.8) than to a linear function ($R^2$= 0.7) of MFR, while SIR showed weaker (linear) correlation with MFR ($R^2$= 0.5). IE values derived from ED BOLD images showed an equivalent correlation with exponential and linear functions ($R^2$= 0.7) of MFR, while SIR showed no correlation to linear or exponential functions of MFR ($R^2$ ~0). Statistical post-hoc power at the significance level of 0.05 was ~1 for all regressions. These results indicate that the myocardial BOLD effect can be more reliably captured with a metric reflecting the size of the affected region (such as the proposed IE) than with a metric reflecting mean intensity changes (such as the conventional SIR). Table 1 lists findings from ROC analysis. IE, derived using ARREAS, shows superior sensitivity and specificity (AUC differences are statistically significant, Table 1) compared to currently used approaches relying on the mean intensity of myocardial segments (SIR).

**Discussion & Conclusions:** BOLD MRI is a compelling approach for evaluating myocardial oxygenation changes due to coronary stenosis. This study proposed, tested, and validated a statistical approach for identifying myocardial territories affected by stenosis in adenosine stress images based on thresholds derived from rest images in canines. Compared to the conventional approach, ARREAS significantly increases the sensitivity and specificity for detecting BOLD changes; and offers the ability to quantify such changes on the basis of a metric that reflects the area of the myocardial territory affected by the stenosis. The proposed method has the potential to rapidly determine the presence of oxygenation anomalies in the myocardium due to coronary artery disease, and provide an unbiased and quantitative imaging biomarker that can enable the assessment of the critical states of stenosis on the basis of BOLD MRI. The method remains to be evaluated in humans.

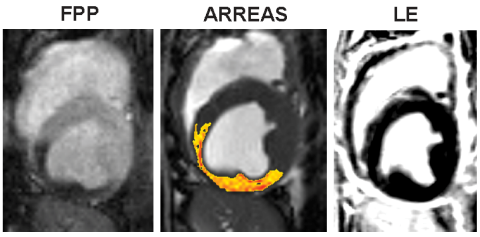


**Fig. 1** Relation between first-pass perfusion (**FPP**), myocardial BOLD image processed using **ARREAS**, and late-enhancement (**LE**) images. FPP image obtained under adenosine stress with critical LCX stenosis and the corresponding BOLD image (processed with the ARREAS method matched to the trigger time of the FPP image) are shown for comparison. LE image acquired (at rest, prior to euthanization) at the same slice position and approximately the same trigger time, confirms the absence of any infarction.

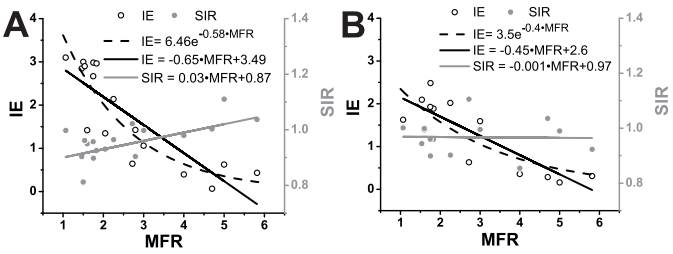


**Fig. 2** Scatter plots and fits of *Ischemic Extent* (IE, **left-hand y-axis**) or *Segment-Intensity Response* (SIR, **right-hand y-axis**) vs. Microsphere Flow Ratio (*MFR*, **x-axis**), derived from BOLD images acquired at end-systole (**A**) and end-diastole (**B**).

**Table 1:** Specificity, Sensitivity, and Area-Under-the-Curve (AUC) based on ROC analysis for IE and SIR at end-systole and end-diastole.

| | ***Ischemic Extent* (IE)** | | ***Segment-Intensity Response* (SIR)** | |
|---|---|---|---|---|
| | **End-Systole** | **End-Diastole** | **End-Systole** | **End-Diastole** |
| **Cutoff** | IE ≥ 2.1 | IE ≥ 1.4 | SIR ≤ 0.93 | SIR ≤ 0.98 |
| **AUC/SE*** | 0.97/0.03 † | 0.88/0.1‡ | 0.83/0.10† | 0.47/0.17‡ |
| **Specificity** | 100% | 85.7% | 87.5% | 42.8% |
| **Sensitivity** | 87.5% | 83.3% | 77% | 83.3% |

* AUC: Area-Under-the-Curve / SE: Standard-Error of AUC metric.
† AUC difference between IE and SIR significant (z=1.68; p=0.045)
‡ AUC difference between IE and SIR significant (z=1.76; p=0.039)

**References:** **(1)** Friedrich et al., Circ 108:2219-2223(2003); **(2)** Shea et al., Radiology 236(2):503-509(2005); **(3)** Dharmakumar et al., Inv. Rad. 42(3):180-188(2007); **(4)** Wilke et al., Magn. Res. Q., 10(4):249-286(1994); **(5)** Tsaftaris et al., ISMRM *2009* #3748; **(6)** Klocke et al., Circ 104:2412-2416 (2001).