Published in final edited form as:
Proc SPIE. 2012 February 23; 2012(8315): . doi:10.1117/12.911672.

Automated Detection of Contractile Abnormalities from Stress-Rest Motion Changes

Shahryar Karimi-Ashtiani[1], **Reza Arsanjani**[1], **Mathews Fish**[4], **Daniel Berman**[2], **Paul Kavanagh1**[1], **Guido Germano**[1,3], and **Piotr Slomka**[1,3]

[1]Departments of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

[2]Cedars-Sinai Heart Institute, Los Angeles, CA

[3]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA

[4]Oregon Heart and Vascular Institute, Sacred Heart Medical Center, Springfield, OR

Abstract

Changes in myocardial function signatures such as wall motion and thickening are typically computed separately from myocardial perfusion SPECT (MPS) stress and rest studies to assess for stress-induced function abnormalities. The standard approach may suffer from the variability in contour placements and image orientation when subtle changes between stress and rest scans in motion and thickening are being evaluated. We have developed a new measure of regional change of function signature (motion and thickening) computed directly from registered stress and rest gated MPS data. In our novel approach, endocardial surfaces at the end-diastolic and end-systolic frames for stress and rest studies were registered by matching ventricular surfaces. Furthermore, we propose a new global registration method based on finding the optimal rotation for myocardial best ellipsoid fit to minimize the indexing disparities between two surfaces between stress and rest studies. Myocardial stress-rest function changes were computed and normal limits of change were determined as the mean and standard deviation of the training set for each polar sample. Normal limits were utilized to quantify the stress-rest function change for each polar map sample and the accumulated quantified function signature values were used for abnormality assessments in territorial regions. To evaluate the effectiveness of our novel method, we examined the agreements of our results against visual scores for motion change on vessel territorial regions obtained by human experts on a test group with 623 cases and were able to show that our detection method has a improved sensitivity on per vessel territory basis, compared to those obtained by human experts utilizing gated MPS data.

Keywords

Coronary artery disease; Regional wall motion; SPECT; Gated study

INTRODUCTION

Myocardial perfusion SPECT (MPS) has found widespread application as the noninvasive modality of choice for diagnosis of coronary artery disease (CAD) [1]. Myocardial ischemia is characterized by abnormalities in the stress study perfusion and function, which were not present during the rest study. Traditionally, differences between perfusion signature values such as sum of perfusion scores (summed stress score (SSS) / summed rest score (SRS)), or total perfusion deficit (TPD), between stress and rest studies are markers of ischemia [2]. However, patients with significant disease such as multi-vessel CAD may have a false negative normal perfusion at least in some vascular territories, due to overall balanced reduction in flow, which may result in equalized global count deficiency, and consequently

no clearly definable defects [3]. Prior studies have identified additional markers, mainly changes in global [4] or regional myocardial functions such as myocardial wall motion and thickening [5] during post-stress imaging, which provide incremental diagnostic value to those provided by perfusion images for identification of patients with severe CAD.

In this work, we developed new myocardial functional changes, specifically stress-rest motion and thickening changes. As a part of this approach, we devised a novel myocardial surface registration method for accurate computation of myocardial functional changes between stress and rest studies. The assessment of functional changes was subsequently performed by direct registration of myocardial walls between stress and rest studies. The advantage of direct myocardial surface registration is that there are no disparities due to independent stress and rest segmentation of the left ventricle (LV). We subsequently compared the overall accuracy of our new proposed method for detection of abnormality in per vessel territory versus those obtained by human expert visual scoring of motion and thickening.

MATERIALS AND METHODS

For the experiments of this study, the Cedars-Sinai suite of software [6] for myocardial quantifications was used for front-end processing tasks such as LV and myocardial surface segmentations.

Myocardial Surface Registration

We used the best ellipsoid fit [7] for myocardial surface point indexing system as shown in Figure 1. Figure 2 shows that best ellipsoid fit provides a coordinate system which represents each sample point of a myocardial surface by a pair of (a, p) integers representing spherical coordinates (azimuth and polar angle). Each point also has a unique radius r determined separately for 2 images. The radius determined for stress and rest images may be different, but a specific location with a and p coordinates should correspond to the same point of the myocardium at stress and rest. The change in motion or thickening determined from end diastolic (ED) and end systolic (ES) image phases at a given location a and p between stress and rest gated images is of clinical interest, because regional wall motion abnormalities have been associated with significant CAD [5]. For extracting precise myocardial function signature changes, it is essential to have an accurate one-to-one mapping between points of myocardial surfaces at ED or ES time frame in the stress and rest studies. Similarly, for accurate computation of functional signatures in stress and rest study, accurate one-to-one mapping between the myocardial surfaces at ED and ES is required. Segmentations of myocardium by best ellipsoid fits are performed independently for the stress and rest studies, which could lead to a disparity between the actual physical locations represented by (a, p) coordinates on the corresponding surfaces. That is, a point represented by the (a, p) polar map coordinates in the stress ES ellipsoid might actually map onto a different (a', p') point represented by the rest ES ellipsoid, as shown in Figure 2.

Figure 2 shows the best ellipsoid fits for the endocardial surfaces at ES time frames for stress and rest studies. To measure the global degree of disparity between their indexing systems, the sum of absolute intensity difference (SAD) was employed;

$$\mathrm{SAD}_{\mathrm{S\_ES,R\_ES}}=\Sigma_{a,p}[\alpha|I_{S\_ES}(a,p)-I_{R\_ES}(a,p)|+\beta|\nabla I_{S\_ES}(a,p)-\nabla I_{R\_ES}(a,p)|] \quad (1)$$

where I_{S_ES} and I_{R_ES} are the intensities (after count normalization) at ES time frame for stress and rest studies, ∇ is the gradient operator, and $0 \leq \alpha, \beta \leq 1$. For this study, the value of α and β were empirically set to 0.1 and 0.9, respectively.

The minimal SAD_{S_ES,R_ES} is achievable when there is an exact one-to-one mapping between the two indexing systems (i.e. a=a' and b=b') and the two surfaces are perfectly registered. To this end, the disparities between indexed points of two ellipsoids can be alleviated by minimizing SAD_{S_ES,R_ES} through adjusting one of the ellipsoids (while the included LV is stationary). This is achieved by searching for the optimal rotation for one of the ellipsoids about its origin. Rotating the ellipsoid about its origin results in another unique set of indices for the myocardial surface which in turn produces a new value for SAD_{S_ES,R_ES}. Therefore, minimizing SAD_{S_ES,R_ES} is equivalent to finding the best indexing set which registers the two myocardial surfaces. A similar procedure was followed to register two surfaces between ED at ES time frames separately for stress and rest studies. In the registration technique, the valve plane location is copied from the stress to the rest studies (or ED to ES time frames) to avoid any indexing range problem induced by mislocalization of the valve plane. In this technique, the sample indices rather than their coordinates were manipulated, and non-rigidity of the myocardium is effectively taken into account. Besides, equation (1) is a global identity with minimal sensitivity to local variability of the perfusion counts, and image artifacts. As a result, the registration was robust against local count changes.

Myocardial Wall Function Signatures

Two types of myocardial functional signatures were evaluated during this experiment, which included stress-rest motion and thickening changes. Motion was characterized as endocardial absolute displacement between ED and ES time frames. Thickening was defined as the percentage of the change in distance between endo- and epicardial walls during the ED to ES time interval. Consequently the stress-rest motion and thickening changes were defined as the difference between stress and rest values for motion and thickening derived from coregistered surfaces. All function signatures were calculated for every (a, p) polar map sample.

Vessel Territory Quantification

For each functional signature, the *Severity Measures* computed for each polar map were averaged over each vessel territory region, establishing the *Territory Severity Measures*. Segmentation of the polar map into vessel territories (i.e., Left Anterior Descending Artery - LAD, Left Circumflex – LCx, Right Coronary Artery - RCA) was performed automatically by Cedars-Sinai software tools [6]. The normal limits for a functional signature *Territory Severity Measure* were derived by calculation of the mean and standard deviation over the training set (as described in a section below). Therefore, for each vessel territory, two sets of *Territory Severity Measure* normal limits were calculated for motion and thickening changes. For each vessel territory, we ran two parallel diagnostic tests with motion and thickening changes, by using the corresponding *Territory Severity Measure* normal limits. To understand how each test was performed, we focus on describing the motion change test as an example. If for a given vessel territory, the stress-rest motion change *Territory Severity Measure* fell within two standard deviations of the mean (mean and standard deviation were already given by *Territory Severity Measure* normal limits for motion change), the test outcome was considered negative and otherwise the test decision was positive for that vessel territory. Thickening changes were estimated in a similar manner. The outcomes of the two tests for each vessel territory (motion or thickening) were then combined by disjunction operator (Logical OR) to comprise *Territory Function Test*

Clinical Validation

We have applied the developed new measures of function change to detect changes in patients with CAD and compared the performance of such automatic changes analysis with visual scoring of motion by experts. For training and validation all cases were selected

consecutively. All patients had undergone exercise or adenosine stress ^{99m}Tc-sestamibi gated MPS. The studies were performed using standard nuclear cardiology ^{99m}Tc-sestamibi rest/stress protocols [9]. All subjects were imaged at 60 min after the administration of ^{99m}Tc-Sestamibi at rest followed by post-stress images taken at 15–45 min after either radiopharmaceutical injection during treadmill testing or adenosine infusion with low-level exercise. Vertex, dual-detector scintillation cameras with low energy high-resolution collimators (Philips Medical Systems, Milpitas, CA), were used to acquire MPS. Tomographic reconstruction was performed by use of the AutoSPECT (Philips Medical Systems).

We have derived normal limits of change for stress-rest motion and thickening changes from training population, which were used to train the system with respect to normal motion and thickening changes. The training normal set consisted of 100 cases with less than 5% likelihood (LLK group) of having CAD based on Diamond and Forrester criteria [8]. They were selected consecutively on the basis of age, sex, pretest symptoms, and electrocardiogram response to adequate treadmill stress testing. For each set, we calculated the normal limits for every (a, p) sample of the polar map by estimating the sample mean and standard deviation of function changes derived from the training set. Deficiencies in myocardial function at stress relative to the rest are markers of ischemic tissues and therefore it is essential for any detection method to quantify such conditions. In order to evaluate the myocardial function, we considered a two-standard-deviation window centered at the mean as the normal (non-ischemic) range for each polar map functional signature. To measure the degree of abnormality, an abnormality *severity measure* was defined. At a polar map, a functional measure e.g. a motion change receives a *Severity Measure* of 0 if it is within the two-standard-deviation window. Similarly, the functional measures between 2–3, 3–4, and beyond 4 standard deviations of the mean are assigned severity measures of 1, 2, and 3 respectively.

The test group consisted of a mixed population of 623 cases with and without CAD conditions. The average age was 64 ± 12 years, 57% were male, and 67% underwent pharmacological stress test. Furthermore, 27% of patients had diabetes mellitus, 64% had hypertension, and 51% had hyperlipidemia. All test patients underwent coronary angiography tests within three months of their SPECT scans and none had any cardiac events during this period. The results of invasive coronary angiography were treated as the gold standard, and a stenosis of 70% was considered significant.

For comparison, motion was scored on a 17 segmental basis by a human expert in all 623 cases. The motion visual scoring was performed separately for stress and rest studies. Differential value of stress and rest visual scores for each segment was employed as the visual motion change scores throughout this study. A 5-point grading system was applied for visual scores, and a segment with visual score greater than or equal to 2 was considered abnormal. Visual segmental scores were then integrated into regional (per vessel) summed scores. For quantification of vessel territories by visual scores, the *Territory Sum of Visual Motion Change Scores* were used, with a sum score larger than 2 being considered as abnormal. Comparison of sensitivity and specificity between groups were made using McNemar's test. For all analyses, P values <0.05 were considered statistically significant.

RESULTS

In Table 1, the means and standard deviations for optimal rotations derived by minimizing equation (1) are presented, which were derived from the normal training group. Figure 3 compares the new automated method based on derivation of the myocardial normal limits of change and the visual motion change scores for detection of motion abnormality in LAD

territory. Figure 3 demonstrates that the sensitivity of our method for motion change ($P < 0.01$) or motion and thickening change ($P < 0.001$) was significantly better for detection of motion abnormality in the LAD territory in patients with high grade LAD stenosis than the visual motion change scores. There was an expected decline in overall specificity for both motion change ($P < 0.01$) and combined motion and thickening change ($P < 0.0001$). Figure 4 compares our newly automated method versus visual motion change scores for detection of abnormalities in the LCX territory. Again, our method had a better sensitivity for detection of CAD in LCX than the visual motion change scores ($P < 0.0001$) in patients with high grade LCX stenosis, however the specificity was again lower ($P <0.0001$). Figure 5 compares our new automated method versus visual motion change scores in the RCA territory. The sensitivity of the automated motion change was not significantly different than the visual motion change scores ($P = 0.2665$) for patients with high grade RCA stenosis, however the sensitivity of the combined motion and thickening was significantly higher than the visual motion change scores ($P < 0.0001$). The specificity of our method was again lower than the visual motion score for identification of abnormality in the RCA territory ($P < 0.0001$).

DISCUSSION

The advent of electrocardiographically gated SPECT images has allowed for calculation of left ventricular ejection fraction as well as the assessment of regional function. The simultaneous evaluation of perfusion and function improves the diagnostic potential of SPECT studies for diagnosis of CAD [3–5]. The importance of functional information is most valuable in patients with multi-vessel disease and balanced ischemia, where up to 20% of patients will have a normal perfusion imaging [10]. Prior studies have demonstrated that regional wall motion changes during post-stress imaging are associated with significant CAD [5]. Regional wall motion change during stress and rest is usually assessed visually. However, visual evaluation may suffer from the variability in contour placements and image orientation when subtle changes between stress and rest scans in motion and thickening could go undiagnosed. By registering the ellipsoid surfaces, we were able to accurately detect these subtle changes, which likely resulted in higher overall sensitivity of our novel method as compare to the visual analysis. Our novel method was able to detect a significantly higher proportion of patients with regional wall motion abnormality in the same region as supplied by obstructive coronary artery. Future studies may combine the findings from our work with the information provided by perfusion imaging to evaluate the overall diagnostic performance of the combined method.

CONCLUSION

In this work, we presented a new technique for myocardial surface non-rigid registration. Registering the surface enabled us to eliminate the polar map indexing disparities between endocardial surfaces of different cardiac cycles and studies (stress and rest). As a result, myocardial wall function signatures – motion and thickening change were accurately computed. For quantification of myocardial wall function signatures, the normal limits were employed as two-standard deviation windows centered at the means. The overall sensitivity of our method for motion change was significantly higher for detection of CAD (with the exception of the RCA region) than the visual motion scores. The combination of motion and thickening change had significantly higher sensitivity in all vessel territories than the visual motion change score. This is a very important finding because prior studies have demonstrated that detection of regional wall motion change during post-stress imaging is associated with severe CAD and provides incremental prognostic information to those provided by perfusion imaging alone[5]. Further studies are needed to evaluate the

diagnostic significance of our new methods and these would combine information provided by our method to those provided by perfusion imaging.

Acknowledgments

This research was also supported in part by grant R01HL089765-02S1 from the NHLBI/NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NHLBI. We would like to thank Arpine Oganyan for editing and proof-reading the text.

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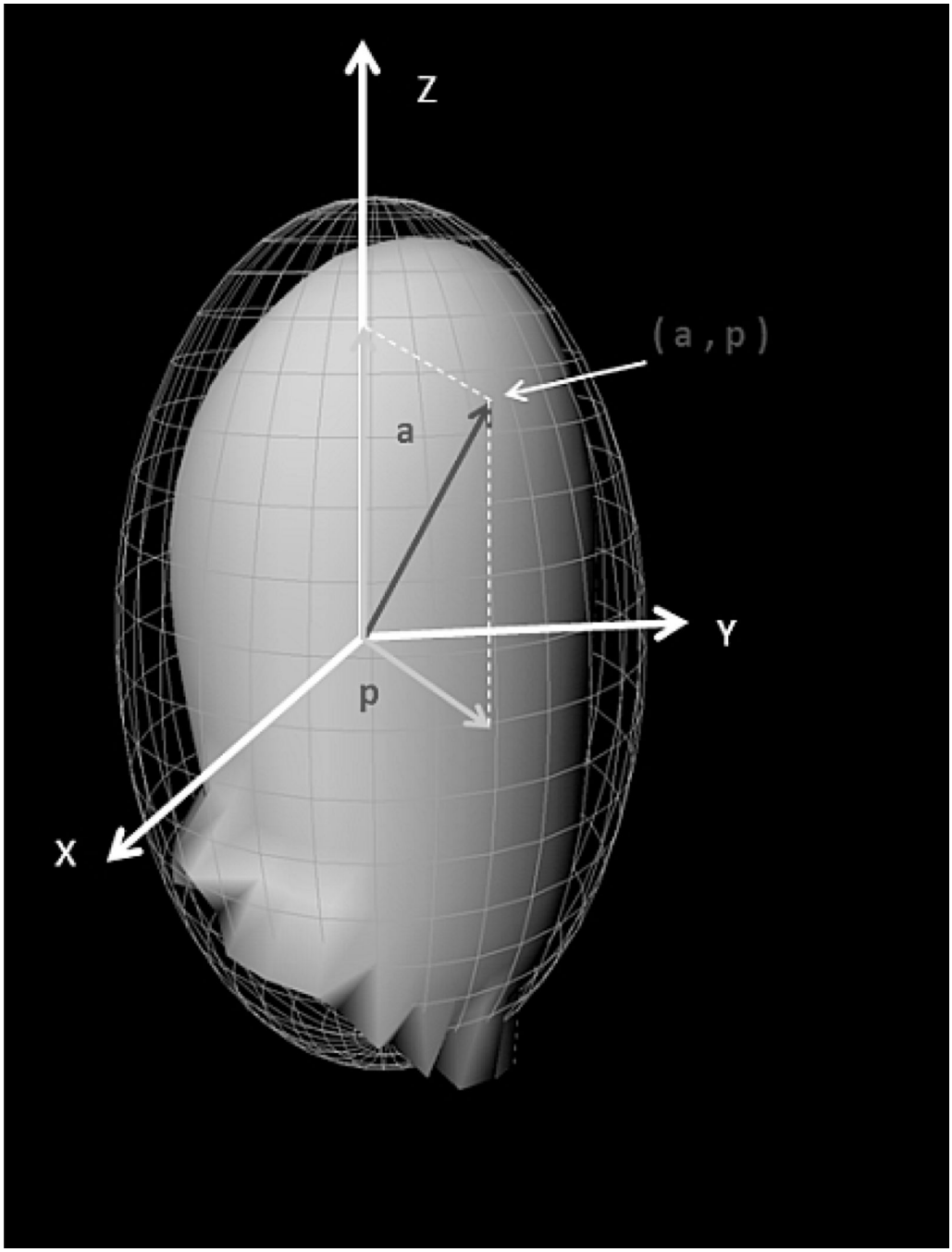

Figure 1.
Left ventricular best ellipsoid fit and its coordinate system for representation of myocardium surfaces.

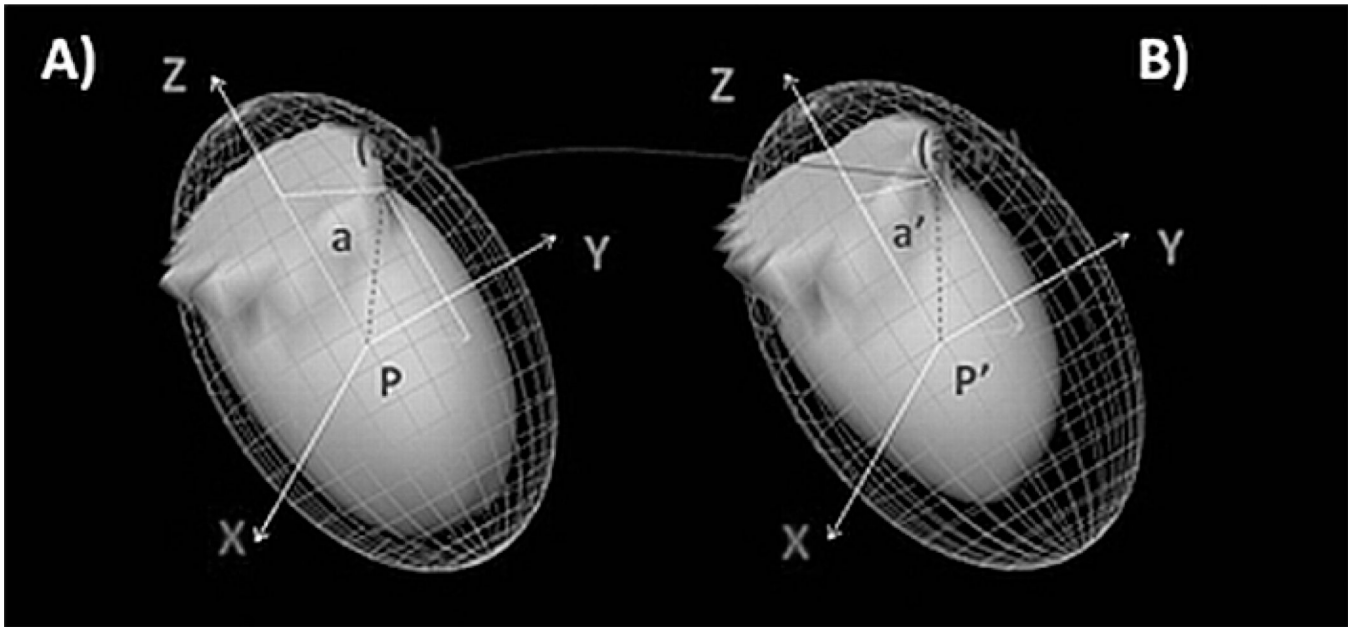

Figure 2.

Segmented endocardial surfaces and their corresponding best ellipsoid fits. A) Stress end-systole (ES), B) Rest end-systole (ES). As a result of independent segmentations of myocardium in stress and rest studies, a point indexed by (a, p) in the stress study may actually be represented by (a', p') indices at rest study. If not compensated by registration methods, this is a potential source of errors for myocardial motion and thickening.

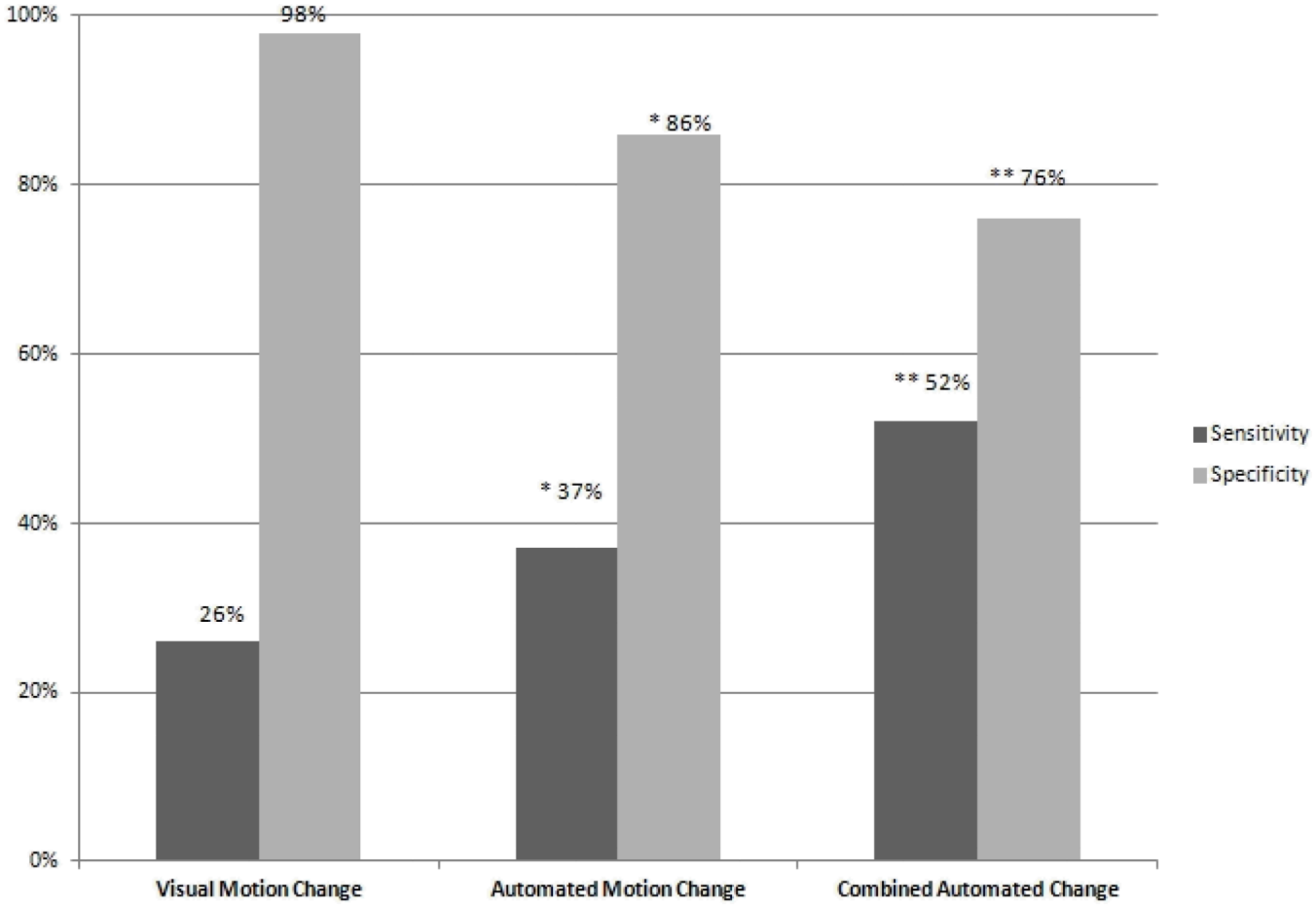

Figure 3.

Sensitivity and specificity for detection of LAD territory abnormality based on *Sum of Visual Motion Change Scores* and our *Function Test* results (motion change, and motion and thickening change) in patients with documented LAD stenosis on invasive coronary angiography. * $P < 0.01$, ** $P < 0.0001$

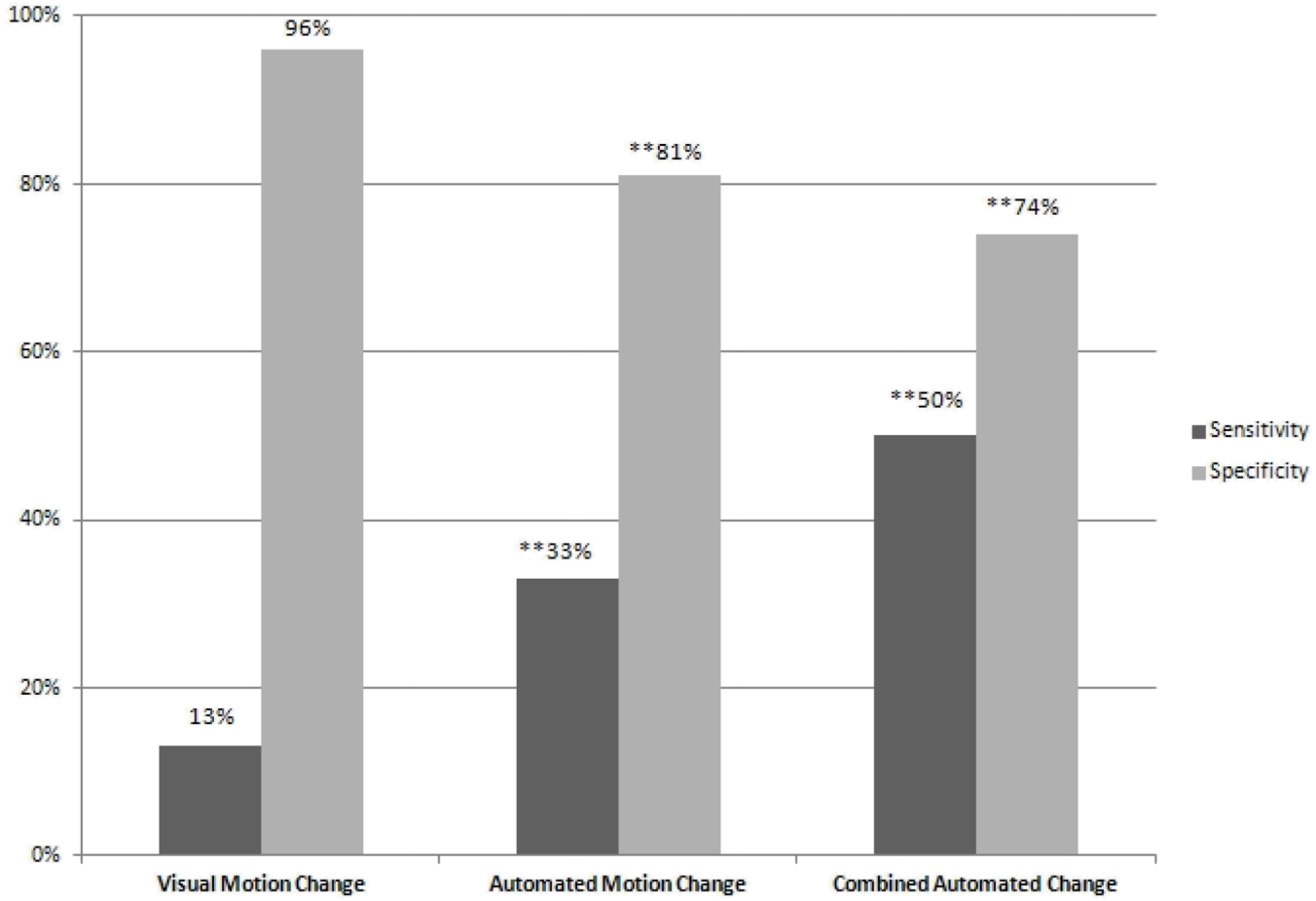

Figure 4.

Sensitivity and specificity for detection of LCX territory abnormality based on *Sum of Visual Motion Change Scores* and our *Function Test* results (motion change, and motion and thickening change) in patients with documented LCX stenosis on invasive coronary angiography. ** $P < 0.0001$

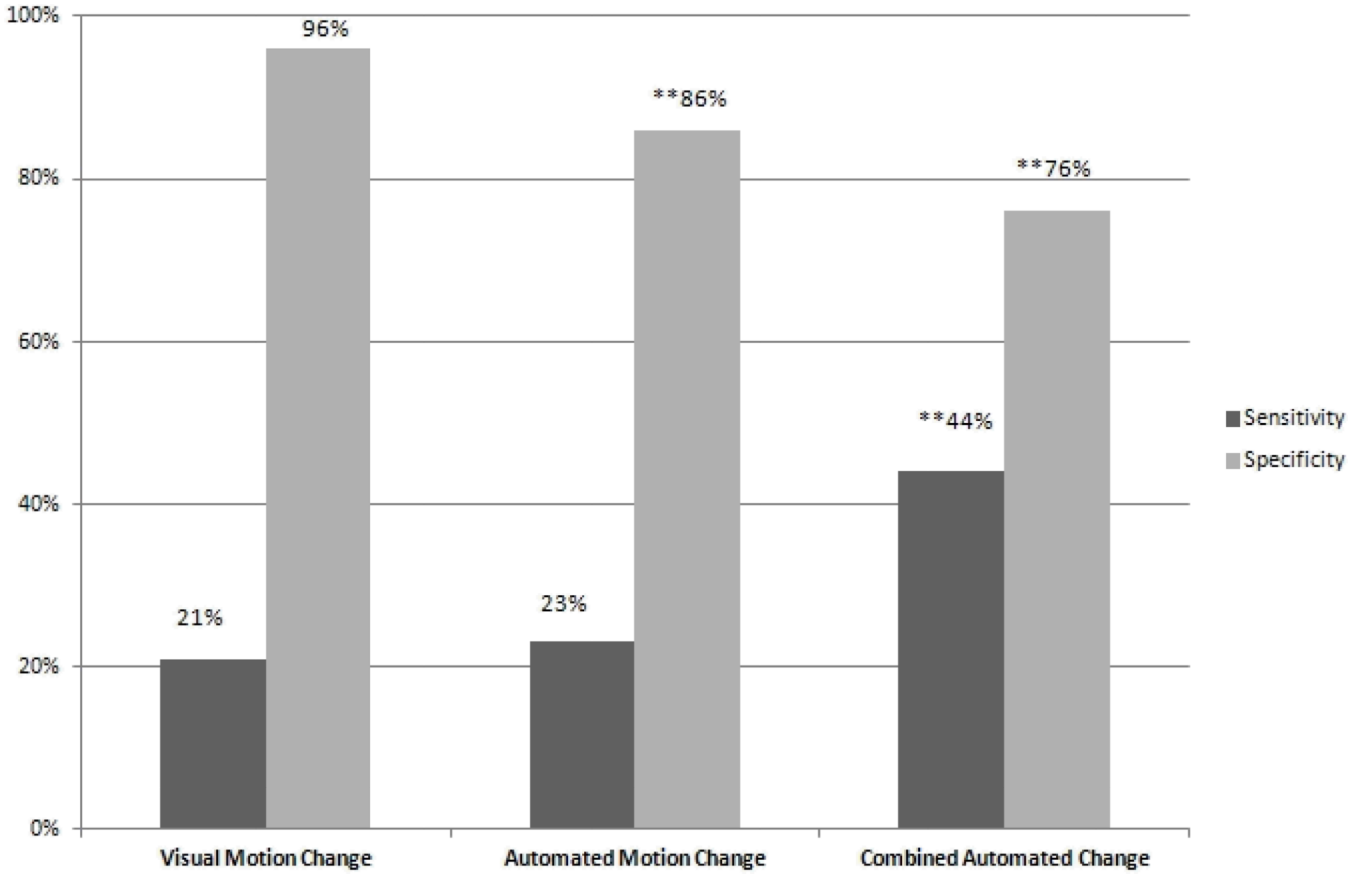

Figure 5.

Sensitivity and specificity for detection of RCA territory abnormality based on *Sum of Visual Motion Change Scores* and our *Function Test* results (motion change, and motion and thickening change) in patients with documented RCA stenosis on invasive coronary angiography. ** $P < 0.0001$

Table 1

Optimal rotation components for endocardial registration for end-diastolic (ED) and end-systolic (ES) for the three different scenarios in this study are listed. The Means and Standard Deviations (SD) were calculated over the training set. Angular measurements are in degrees.

	ED To ED, Stress			ED To ES, Rest			ED to ED, Stress to Rest		
	X	Y	Z	X	Y	Z	X	Y	Z
Mean	0	−1	3	1	−1	2	−3	−1	−2
SD	±9	±9	±7	±5	±4	±3	±7	±7	±7