Clinical Validation of an Automated Technique for MRI Based Quantification of Myocardial Perfusion

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Abstract

We have recently developed an automated technique using noise-based level-set methods and non-rigid registration for endocardial and epicardial border detection as a basis for perfusion quantification from cardiac magnetic resonance (CMR) images. The goal of the present work was to validate this technique against conventional manual analysis both directly and using quantitative coronary angiography as reference for significant disease (stenosis >50%). We studied 27 patients undergoing contrast-enhanced CMR imaging (1.5T) at rest and during adenosine stress. Contrast enhancement time-curves were constructed and used to calculate a number of perfusion indices. Measured segmental pixel intensities in each frame correlated highly with manual analysis (r=0.95). Bland-Altman analysis showed small biases (1.3 at rest; 0.0 at stress) and narrow limits of agreement (±13 at rest; ±14 at stress). The derived perfusion indices showed the same diagnostic accuracy as manual analysis (AUC up to 0.72 vs. 0.73). These results indicate that our automated technique allows fast detection of myocardial ROIs and quantification of stress-induced perfusion abnormalities as accurately as manual analysis.

1. Introduction

Although cardiac magnetic resonance (CMR) is an attractive alternative for quantitative evaluation of myocardial perfusion, it relies on the definition of myocardial regions of interest (ROIs). This is usually achieved by manually drawing ROIs in one frame and then adjusting their position and shape on subsequent frames to compensate for cardiac motion and deformation due to respiration [1]. This tedious, time-consuming and potentially inaccurate methodology has been hindering widespread clinical application of imaging-based quantification of myocardial perfusion. Unfortunately, the development of automated techniques has been difficult because of the extreme dynamic nature of contrast-enhanced image sequences and out-of-plane cardiac motion [2]. We recently developed an automated technique for myocardial ROIs definition based on statistical level-set methods and non-rigid registration approaches [3].

The goal of the present work was to validate this technique against conventional manual analysis using images obtained in patients undergoing pharmacological stress CMR testing. To achieve this goal, we compared the diagnostic accuracy of the automatically and manually derived perfusion indices against quantitative coronary angiography (QCA), which was used as the reference for presence and severity of coronary artery disease (CAD).

2. Methods

2.1. Population

Twenty-seven adult subjects (age 64±13 yrs, 20 males) were studied using CMR imaging. Exclusion criteria were standard contraindications to CMR imaging with gadolinium DTPA (Gd-DTPA), and contraindications to vasodilator agents. All of these patients, based on abnormal single-photon emission computed tomography, were also referred for coronary angiography, which was performed within 30 days following CMR. Patients were excluded if they had a recent myocardial infarction, or were older than 85 years of age.

2.2. Imaging

Short-axis images were obtained (Siemens 1.5T scanner) at 3 levels of the left ventricle (~50 frames per level) using a hybrid gradient echo/echo planar imaging sequence (nonselective 90° saturation pulse followed by a 80 ms delay, voxel size ~ 2.8 x 2.8 mm, slice thickness 8

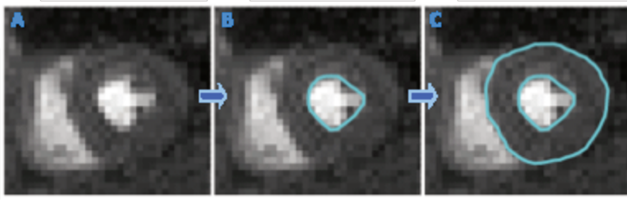

Figure 1. Main steps in myocardial segmentation: A) reference frame selection, B) endocardium segmentation, C) epicardial segmentation.

mm, flip angle 25°, TR = 5.6 to 6.2 ms, TE=1.3 ms). Imaging was performed twice during the first pass of two Gd-DTPA boluses: first using a low dose of contrast (0.0075 mmol/kg at 4 ml/sec) to measure contrast enhancement in the LV cavity without saturation, and then using a standard dose (0.075 at 4 ml/sec) to measure intramyocardial contrast. Patients were instructed to hold their breath as long as possible. Stress imaging was performed starting 2 to 3 minutes after initiation of adenosine (Adenoscan, Astellas Pharma) intravenous infusion at a rate of 140 µg/kg/min. Resting images were obtained 10 minutes after stopping adenosine infusion.

2.3. Automated image analysis

For each slice, the first step consisted of manual placement of a seed point inside the left ventricular (LV) cavity in a random frame. The second step was the automated selection of the best frame for endo- and epicardial detection, which was achieved by tracking over time the pixel intensity in the vicinity of the seed point and identifying the frame in which the intensity reaches 95% of its maximum. In this reference frame (figure 1A), the endocardial boundary was automatically detected using a statistical region-based level-set algorithm, which takes into account the noise distribution in the image [4]. The computed boundary underwent a curvature-driven regularization motion specifically designed to include the papillary muscles inside the LV cavity (figure 1B). Then the epicardial boundary was automatically detected using an edge-based level-set algorithm [5] which searches the image from the endocardium outwards and identifies the epicardium. Finally, the epicardial boundary was also regularized with a modified curvature motion (figure 1C).

Non-rigid registration of the computed boundaries onto the other frames of the sequence was then achieved by a multi-scale extension of two-dimensional normalized cross-correlation, to compensate for cardiac translation and deformation as a result of out-of-plane motion. Subsequently, contour adaptation was performed as a final step of boundary refinement using again the Malladi-Sethian level-set model (figure 2). Templates were updated for each consecutive frame to take into account the changes in pixel intensity occurring during the passage of the contrast bolus.

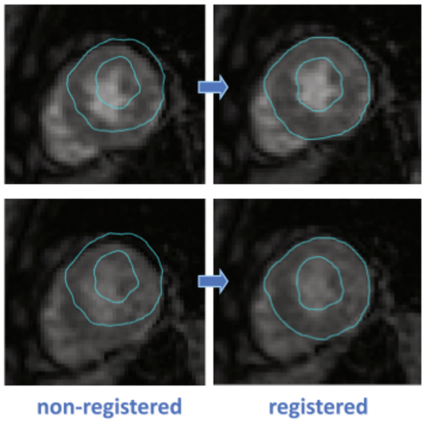

Figure 2. Non rigid image registration: the initial endo- and epicardial contours (left) are shifted and deformed in each frame to match the position and shape of the LV (right).

2.4. Quantification of contrast dynamics

To allow analysis of regional perfusion, the myocardial ROI, defined as the area between the detected endo- and epicardial contours, was divided into 16 wedge-shaped segments (6 at the basal and mid-ventricular levels and 4 at the apical level), according to the standard segmentation model. Then pixel intensity was measured in each segment over time, resulting in contrast enhancement curves throughout the image sequence.

From each myocardial curve obtained at both rest and stress the following indices were calculated: (1) the peak-to-peak amplitude, reflecting the concentration of contrast per unit volume of myocardium, (2) the slope of the contrast enhancement phase, reflecting contrast inflow rate, calculated using the linear regression analysis of the upslope portion of the curve, and (3) the product of the amplitude and slope. In addition, each index was normalized by its respective LV cavity value, which was measured from the low contrast dose image sequence (in a small circular ROI manually placed near the center of the cavity) and multiplied by 10 to compensate for differences in doses. Stress to rest ratio was calculated for each index (both non-normalized and cavity normalized) to reflect perfusion reserve of these indices.

2.5. Validation against manual tracing

To validate our automated technique, myocardial segments were manually traced using commercial software (Argus, Siemens), resulting in segmental mean pixel intensity over time. Mean pixel intensity in each automatically defined and manually traced segment was compared frame-by-frame for the resting images and separately for stress images. Perfusion indices were calculated from these curves the same way as from the automatically generated curves. These perfusion indices were compared between the automatically and manually

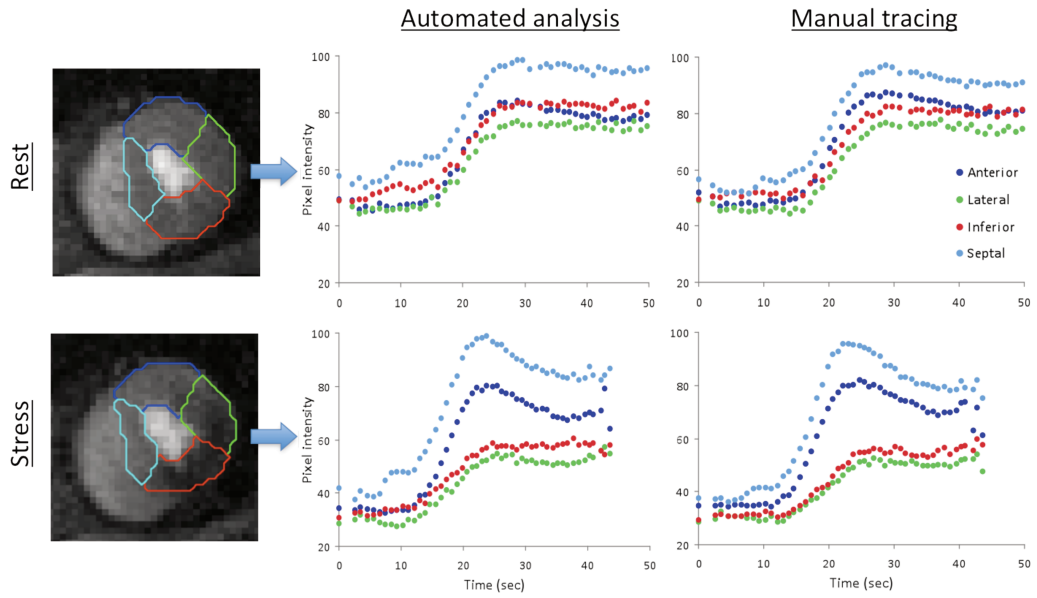

Figure 3. Contrast enhancement curves obtained with the proposed automated technique (center) and through manual tracing (right) in a patient with a stress-induced perfusion defect (left). The two techniques result in virtually identical curves.

generated contrast enhancement curves. Inter-technique comparisons were performed using linear regression analysis with Pearson's correlation coefficients and Bland-Altman analysis of biases and limits of agreement.

Diagnostic accuracy of the automated analysis was evaluated side-by-side with the manual technique by comparing both methods against QCA as a reference for the presence and severity of CAD. Each myocardial segment was classified as normal or abnormal based on the presence, location and severity of stenosis detected in the relevant coronary artery. Stenosis >50% luminal narrowing was considered as evidence of significant CAD. This classification of myocardial segments was performed by an experienced interventional cardiologist, and was used as a reference, against which an abnormality threshold was calculated in each segment for each perfusion index using receiver operating characteristic (ROC) analysis. In order to account for differences in the anatomic location of each segment, these abnormality thresholds were allowed to vary from segment to segment. For each index, area under ROC curve was averaged for the 16 myocardial segments.

3. Results

Time required for automated analysis of a complete perfusion sequence in one slice was <1 minute on a standard PC and resulted in myocardial boundaries that were judged accurate. Contrast enhancement curves clearly showed the typical pattern of first-pass perfusion both rest and stress. Figure 3 shows an example of an image obtained in a patient with a stress-induced perfusion abnormality in the inferior and lateral walls (bottom left) as depicted by the automatically generated contrast enhancement curves (center). This finding was confirmed by manual technique, which showed almost identical curves (right).

Excellent inter-technique agreement was noted both at rest and stress comparing frame-by-frame segmental pixel intensity values obtained automatically and manually, as reflected by correlation coefficients of r=0.95 (both at rest and stress), regression lines near unity (y=0.95x+5 at rest, y=0.95x+2 at stress), as well as virtually zero biases (1.3 at rest, 0.0 at stress) and reasonably narrow limits of agreement (±13 at rest, ±14 at stress). Perfusion indices measured by the two techniques also showed good agreement (Table 1), as reflected by high correlations, small biases and relatively narrow limits of agreement for most indices. Table 2 shows the summary of the ROC analysis for perfusion indices obtained by both the automated and manual techniques on a segment-by-segment basis. Importantly, the diagnostic accuracy of the automated analysis was similar to that of the manual technique across all perfusion indices studied, as reflected by the segmental AUC values.

4. Discussion and conclusions

This study aimed at validating a recently developed automated technique for the quantification of intra-myocardial contrast on CMR images against conventional manual analysis and demonstrated its clinical utility. Manual tracing is an operator-dependent, cumbersome and error- prone technique, which requires often at least 10 min for the analysis of a single perfusion image sequence. These factors have prevented the widespread of

Table 1. Results of the comparisons between perfusion indices derived from automatically and manually generated contrast enhancement curves: linear regression analysis with Pearson's correlation coefficient (y = ax + b and r) and Bland-Altman analysis of inter-technique differences (bias ± SD).

		r	a	b	Bias	SD
Amp	stress	0.90	0.89	4.8	0.25	6.5
	stress/cav.	0.92	1.05	-0z.0013	0.0030	0.015
	stress/rest	0.87	0.88	0.22	0.016	0.55
	stress/cav. / rest/cav.	0.75	0.76	0.48	0.070	0.68
Slope	stress	0.94	0.88	0.46	-0.18	0.88
	stress/cav.	0.94	1.05	-0.0017	0.00029	0.0080
	stress/rest	0.81	0.78	0.57	0.0069	1.10
	stress/cav. / rest/cav.	0.72	0.93	0.26	0.14	0.89
Amp*Slope	stress	0.90	0.83	38	-17	104
	stress/cav.	0.90	0.88	0.00030	0.00000	0.0020
	stress/rest	0.83	0.90	0.32	-0.10	4.10
	stress/cav. / rest/cav.	0.72	0.88	0.55	0.21	2.10

Table 2. Results of the ROC analysis for perfusion indices obtained by both the automated and manual techniques, expressed as area under curve (AUC).

		AUC	
		Auto	Man
Amp	stress	0.70	0.71
	stress/cav.	0.58	0.59
	stress/rest	0.58	0.58
	stress/cav. / rest/cav.	0.55	0.55
Slope	stress	0.71	0.70
	stress/cav.	0.54	0.54
	stress/rest	0.56	0.58
	stress/cav. / rest/cav.	0.53	0.57
Amp*Slope	stress	0.72	0.73
	stress/cav.	0.59	0.60
	stress/rest	0.59	0.58
	stress/cav. / rest/cav.	0.56	0.57

CMR perfusion quantification in the clinical environment, despite its potential diagnostic value.

On the other hand, typical CMR perfusion images are characterized by relatively low spatial resolution, high noise levels, and in- and out-of-plane cardiac motion, as well as rapid and extreme changes in brightness and contrast of the different image components, which are all factors hampering the development of an automated technique for dynamic myocardial ROIs definition. However, the results of this study show that the proposed technique is able to generate contrast-enhancement curves that are well in agreement with the manually extracted ones. Moreover, the diagnostic accuracy of the two techniques, when using QCA as reference for presence and severity of CAD, is virtually the same.

In summary, our technique allows fast, automated, user-friendly and accurate measurement of intramyocardial contrast enhancement from CMR images, and may thus address the strong clinical need for quantitative evaluation of myocardial perfusion.

References

[1] Wilke NM, Jerosch-Herold M; Zenovich A, Stillman AE, Magnetic resonance first-pass myocardial perfusion imaging: clinical validation and future applications. J Magn Reson Imaging 10:676-685; 1999.

[2] Adluru G, DiBella EV, Schabel MC, Model-based registration for dynamic cardiac perfusion MRI. J Magn Reson Imaging 24:1062-1070; 2006.

[3] Tarroni G, Patel AR, Veronesi F, Walter J, Lamberti C, Lang RM, Mor-Avi V, Corsi C, MRI-based quantification of myocardial perfusion at rest and stress using automated frame-by-frame segmentation and non-rigid registration. IEEE Transac Comput Cardiol 37:1-4; 2010.

[4] Corsi C, Veronesi F, Lamberti C, Bardo DME, Jamison E, Lang RM, Mor-Avi V, Automated frame-by-frame endocardial border detection from cardiac magnetic resonance images for quantitative assessment of left ventricular function: Validation and clinical feasibility. J Magn Reson Imaging 29:560-568; 2009.

[5] Sethian JA, Level set methods and fast marching methods. Cambridge: Cambridge University Press; 1999.

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