Effect of BOLD Contrast on Myocardial Registration

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Introduction: A new contrast and stress-free approach for detecting myocardial ischemia has been recently demonstrated using Cardiac Phase-resolved Blood Oxygen-Level-Dependent (CP-BOLD) MRI.[1] To identify the presence of disease, CP-BOLD relies on the observation that myocardial signal intensity varies as a function of cardiac phase and is modulated in the presence of ischemia. Currently, only a few frames (i.e., images) of the cine acquisition are used and segmental analysis is employed.[1] Thus, the ability to characterize transmural effects is potentially lost.[2] Automated analysis approaches, which can obtain pixel-level determination of ischemia, are desirable since they may lead to improved accuracy in detection of disease. To achieve this, precise non-linear registration among the frames (the cardiac phases) in the cine stack would be required.

Purpose: We hypothesize that BOLD contrast affects the accuracy of non-linear registration algorithms. In this work, the accuracy of the current state-of-the-art methods is tested on cardiac CP-BOLD and standard Cine MRI to evaluate the effects of BOLD contrast in health and disease.

Methods: Imaging Studies: Flow- and motion-compensated 2D short-axis CP-BOLD[2] and standard Cine stacks were acquired within few minutes of each other along the mid ventricle in 10 canines at baseline and under severe LAD stenosis. Imaging studies were performed on a 1.5T Espree (Siemens Healthcare). T_R/T_E was 2.5/1.3ms for standard Cine and 6.2/3.1ms for CP-BOLD, respectively, while keeping the other parameters constant (spatial resolution=1.2x1.2x8 mm^3, flip-angle=70°, ~25 frames per cardiac cycle). [1] The process described below is repeated on the same subjects, using the CP-BOLD or standard Cine acquisition under baseline conditions (without LAD stenosis) and ischemia (with LAD stenosis). A matched design is carried out to evaluate the effects of image contrast (across imaging frames under baseline and ischemia), with minimal bias from anatomical differences. Image Registration: The following registration algorithms, which perform affine and non-linear registration to overcome the complex myocardial motion were identified: Alessandrini[3], ANTs[4], BunwarpJ[5], Diffeomorphic Demons (dDemons)[6], DROP[7], and Free Form Deformations (FFD)[8]. Parameters and settings were optimized for each method, and results are reported based on those. Two registration set-ups are explored: ***A*** *[Minimal cardiac motion]* registration of the first frame (fixed) and the last frame (moving) in the acquisition, which typically reflect minimal motion (diastole), and can thus evaluate more accurately the effects of BOLD contrast and the presence of disease; ***B*** *[Larger cardiac motion]* registration of each frame in the stack (moving) throughout the cardiac cycle to the first frame (fixed) in the stack, and thus investigate the effect of different regularization terms and similarity metrics in capturing larger motion. Statistical analysis: To evaluate registration accuracy, in lieu of cross-correlation or squared error metrics obtained on the whole frame, myocardial segmentation accuracy, which has been shown to be a more suitable metric for this purpose[9], was used. Using manual delineations of the myocardium provided by experts, the myocardial mask from the moving frame to the fixed frame was propagated using the registration field, and its overlap with the ground truth mask of the fixed frame was measured using the Dice overlap metric. Larger overlap indicates greater recovery of myocardial motion. For set-up ***A***, this process is repeated twice, interchanging the fixed/moving frames for each subject; thus, two accuracies were obtained. For set-up ***B***, average accuracy in the stack is reported for each subject. Multiple paired t-tests were used to evaluate the effect across presence of ischemia and acquisition type, pooling measurements for all registration algorithms.

Results: Dice accuracies of the set-up ***A*** are presented in Table 1. BOLD contrast in CP-BOLD affects average registration accuracy significantly when compared to standard Cine in both baseline ($^{\#}$, $p<0.001$) and ischemia ($^{\$}$, $p<0.001$). The results of set-up B are shown in Table 2. Observe that it is harder to compensate for larger cardiac motion (88±7 (set up A) vs, 66±9 (set up B), for the standard Cine under baseline). Again, BOLD contrast negatively affects segmentation accuracy when registering the full cardiac cycle at baseline ($^{\#}$, $p<0.001$) or in the presence of ischemia ($^{\$}$, $p<0.001$). To provide a visual example of how BOLD contrast and ischemia affect the registration of a single algorithm (Alessandrini), in registering frames in the set-up **A**, the displacement vectors of those registrations are shown color-coded in Fig. 1. Under baseline conditions, where cardiac motion should be minimal between diastole, the algorithm finds small and consistent displacements throughout the myocardium; however, when BOLD contrast is present (as in CP-BOLD) greater variability is observed. Under ischemia greater regional variability is observed both in standard Cine and CP-BOLD, consistent with the expected changes in cardiac contractility in the presence of ischemia (from LAD stenosis).

Discussion: The nonlinear registration algorithms employed in this study perform significantly worse in the presence of variations in signal intensity due to the presence of BOLD contrast across cardiac cycle at baseline and ischemia. Two different evaluation set-ups were used to highlight these challenges and to isolate the confounding effects of cardiac motion. In particular, while disease affects registration accuracy, the presence of BOLD contrast affects accuracy to a greater extent.

Conclusion: State-of-the art methods for non-linear registration of the myocardium are not capable of accurately registering frames in CP-BOLD MRI, and recover cardiac motion. While most algorithms perform adequately when standard Cine MRI data are used, when BOLD contrast is present, their performance deteriorates significantly. This study underlines the need for developing new non-linear registration approaches that are capable of dealing with cardiac phase and spatially dependent intensity variations due to the BOLD contrast. The incorporation of such algorithms in the analysis of CP-BOLD MRI can improve the current capabilities of accurately characterizing ischemia on the basis of CP-BOLD MRI.

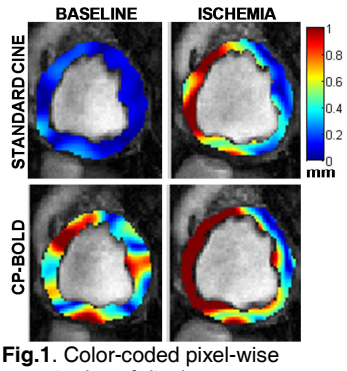

Fig.1. Color-coded pixel-wise magnitudes of displacement vectors in mm overlaid on the original images within the myocardium.

Table 1. Dice (%) overlap (mean±std) for registration for set-up A.

	Baseline		Ischemia	
Methods	**Cine**	**CP-BOLD**	**Cine**	**CP-BOLD**
Alessandrini[3]	90±6	70±10	85±6	62±10
ANTs[4]	90±6	63±9	79±7	58±7
BunwarpJ[5]	85±7	61±11	77±9	61±9
dDemons[6]	90±8	66±7	78±9	65±8
DROP[7]	92±4	67±8	86±4	65±8
FFD-SSD[8]	87±6	67±8	81±7	63±7
FFD-MI[8]	87±7	67±8	74±6	62±7
Average:	88±7	56±13$^{\#}$	80±8	62±8$^{\$}$

Notes: $^{\#}$ denotes statistically significant differences ($p<0.001$) found with the paired t-test comparing average accuracy among all algorithms between CP-BOLD and Standard Cine in baseline. $^{\$}$ denotes the same but under ischemia.

Table 2. Dice (%) overlap (mean±std) for registration for set-up B.

	Baseline		Ischemia	
Methods	**Cine**	**CP-BOLD**	**Cine**	**CP-BOLD**
Alessandrini[3]	60±15	41±9	58±7	41±12
ANTs[4]	62±15	36±9	62±10	36±9
BunwarpJ[5]	47±14	35±7	59±7	33±7
d Demons[6]	55±12	44±8	58±9	38±10
DROP[7]	57±12	40±10	59±12	38±8
FFD-SSD[8]	52±11	38±9	49±12	36±7
FFD-MI[8]	57±12	37±10	55±9	32±5
Average:	66±9	38±9$^{\#}$	57±10	36±13$^{\$}$

Notes: $^{\#}$ denotes statistically significant differences ($p<0.001$) found with the paired t-test comparing average accuracy among all algorithms between CP-BOLD and Standard Cine in baseline. $^{\$}$ denotes the same but under ischemia.

References: (1) Tsaftaris et al., *JMRI* 35(6):1338-48 2012; (2) Tsaftaris et al., *Circ Cardiovasc Img* 6(2):311-9 2013; (3) Alessandrini et al., *IEEE TIP*, 22(3):1084-1095 2013; (4) Avants et al., *MedIA* 12(1):26-41 2006; (5) Arganda-Carreras et al., *LNCS*:85–95 2006; (6) Vercauteren et al., *MICCAI* 39:N319-326 2007; (7) Glocker er al., *MedIA* 12(6):731-741 2007; (8) Rueckert et al., *IEEE TMI* 18(8):712-731 1999; (9) Christensen et al., *WBIR, LNCS* :128-135 2006.