Temporal and Spatial Variation of Baseline Myocardial BOLD Signal Intensity in Cardiac Phase-Resolved BOLD MRI: A Potentially Revealing Insight into Dynamic Changes in Myocardial Oxygenation

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Introduction: Cardiac Phase resolved Blood Oxygen Level Dependent (CP-BOLD) MRI is a recently developed approach for examining BOLD changes and wall motion in a single cine acquisition. With this technique, myocardial BOLD signal intensity can be obtained as a function of cardiac phase. Early findings have suggested that the timeseries extracted from different segments of the myocardium in CP-BOLD imaging appear shifted relative to one another (as shown in an exemplary case, Fig. 1) and that such variations may be explained on the basis of phasic differences in coronary blood flow.[1-3] However, whether these shifts are consistently evident has not been examined rigorously.

Purpose: In this work, we demonstrate the existence of the BOLD signal intensity shifts between myocardial segments (i.e., spatial) using a data-driven temporal pattern recognition method.

Methods: Imaging Studies: Flow and motion compensated 2D short-axis CP-BOLD[4] images were acquired along the mid ventricle in 11 canines at baseline conditions on a 1.5T Espree (Siemens Healthcare) with the following scan parameters: spatial resolution=1.2x1.2x8mm[4], flip-angle=70°, temporal resolution=37.2ms and T_R/T_E =6.2/3.1ms. Image Processing: Myocardial borders were traced[5] in all phases and then segmented in 24 radially consecutive segments (subdividing each of the 6 segments of the AHA model in 4). Based on myocardial delineation, end-systolic (ES) and end-diastolic (ED) images were identified. For each myocardial segment, a CP-resolved timeseries was obtained. All available timeseries were spline interpolated to have length 30, equal to the average number of images in the cine acquisition (30±4) and were columnwise arranged in the matrix Y, 30x264 (24 timeseries from each of the 11 subjects). Signal-to-noise ratio (SNR) was estimated[6] by $SNR=20\cdot\log_{10}(0.655\cdot\mu_t/\sigma_n)$, where μ_t is the average myocardial intensity and σ_n the estimated standard deviation of the noise in background (air). To isolate the presence of shifts among segments we pre-aligned the timeseries from different subjects such that ES occurs at the 10th point over the 30 of the cardiac cycle. The proposed approach follows the classical treatment of testing the presence of shifts in timeseries: pick a template and correlate it (and all of its shifts) with each timeseries, and build a statistical test for significance by keeping the largest correlations. Our method is slightly different since we used a circulant dictionary approach[7] to decompose Y in a shift-invariant manner, whilst at the same time learning the template and performing all possible correlations. We found a circulant matrix C (30x30) with columns called atoms, where the first atom is the learned pattern (see Fig. 2) and all its consecutively downshifted versions are stored in the other columns. In this way, each timeseries in Y was approximated only by one weighted shifted pattern (Y≈CX, where X is the weight matrix, having one non-zero value per column). By summing the squared values of the elements in each row of X, the importance distribution **I** was defined, expressing the energy carried by each atom (or equivalently shift) in the reconstruction of Y. When normalized by its sum, it has been seen as a probability distribution function (PDF, summing to 1). Statistical analysis: *Identifying the presence of shifts*: To demonstrate the presence of shifts we used the Kolmogorov-Smirnov (KS-test) to evaluate the statistical difference between the cumulative distribution functions (CDF) of **I** obtained from the real dataset versus those obtained by repeating the process above with synthetic null datasets as inputs, composed of a single pattern (i.e., no shifts in the data) and added noise of variable SNR. *Identifying the number of shifts present:* To identify the number of shifts, we devised a fitness function *f(n)* that outputs a confidence measure, based on **I**, for each possible value of *n* (1 to 30), the consecutive most important shifts (i.e., the ones that contribute to the shift structure in the dataset) used in the reconstruction of Y. We weighed the reconstruction accuracy of Y (to penalize weakly circulant data), the energy carried by the *n* most important consecutive atoms (to promote local shift structure) and the correlation between the *n* selected atoms with a synthetic case in which all the importance is equally distributed among *n* atoms (to favor the situations in which *n* consecutive shifts are equiprobable). Thus, we would expect this fitness to reach a maximum of 1 when only consecutive equiprobable shifts of a single pattern exist. To obtain statistical significance, we compared *f(n)* between real and null (absence of shift) datasets. A Monte Carlo simulation was used to perform t-tests between the real data and *N*=100 different realizations of null datasets with the same SNR as real data. Finally, a simulation at low SNR was performed to identify noise levels for which the fitness finds the same number of shifts among null and real data; for the same *n*, fitness values are then compared.

Results: The KS-test confirmed that the real data exhibited a shift structure: when SNR≥16dB (the estimated SNR of real data is 21.5dB), the significance is $p<0.02$. Fitness analysis of real data showed $n=6$ atoms with $f_{MAX}=0.49$ (see Fig. 3). Monte Carlo analysis ($N=100$ null datasets using 1 atom, SNR=21.5dB) showed that the fitness always correctly identifies $n=1$ atom in null reconstruction. By varying the SNR in these null datasets expressing $n=1$ shift, if 3≤SNR≤8dB the fitness identifies $n=6$ shifts with $f_{MAX}=0.28$, a much lower value with respect to the one obtained in the real data (0.49). Since the SNR of the real data is 21.5dB, we can confirm that the findings are not due to the presence of noise, but due to actual shifts. Thus, if 30 images are available from the cine acquisition on average approximately 6 shifts are expected to exist in the baseline case.

Discussion: Our results suggested that there exist statistically identifiable phasic differences in BOLD signal intensity extracted with the CP-BOLD approach. A limitation of this is the need to interpolate to accommodate for variable timeseries length. While this study utilized non-invasive imaging, it is the first to demonstrate rigorously the existence of such phasic differences. Previous studies using flow probes in swine and canines did identify such phasic differences invasively at the coronary level.[3] The lack of this invasive validation in the same subject is a limitation of the current work. In this paper, to show phasic differences we utilized a pattern recognition method that identifies and learns a template, for which the maximum correlations between the timeseries and all the possible shifts were obtained. Currently this template driven approach is the state-of-the-art in shift identification.

Conclusions: Phasic differences were identified in CP-BOLD derived signal intensities among different segments. These findings suggest that image processing algorithms for automated detection of ischemic territories on the basis of CP-BOLD should consider such differences in their models.

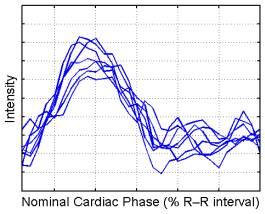

Fig. 1. Timeseries extracted from myocardial segments of a canine at rest.

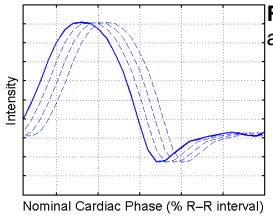

Fig. 2. The identified pattern is shown (solid) along with three representative shifts (dotted).

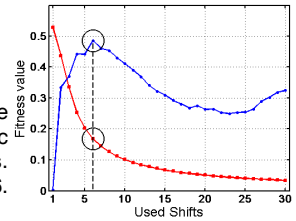

Fig. 3. Fitness values with respect to shifts in the dataset obtained from real (blue) and synthetic (red) data, at SNR=21.5dB without shifts. Observe the difference at *n*=6.

References: (1) Tsaftaris et al., *JMRI* 35(6):1338-48 2012; (2) Tsaftaris et al., *Circ Cardiovasc Img* 6(2):311-9 2013; (3) Ootaki et al., Med. Sci. Monit., 14(10):193-7 2008; (4) Zhou et al., *JMRI* 31(4):863-71 2010; (5) Tsaftaris et al., *ICIP*:2980–3 2008; (6) Firbank et al., Phys. Med. Biol. 44:N261-4 1999; (7) Rusu, Dumitrescu, Tsaftaris, *IEEE SPL* 21(1):6-9 2014.