Unsupervised Ischemia Detection at Rest with CP-BOLD Cardiac MRI: A Simulation Study Employing Independent Component Analysis

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Introduction: Cardiac-phase resolved Blood Oxygen-Level-Dependent (CP-BOLD) MRI is a new approach capable of evaluating an ongoing ischemia without the need for provocative stress or contrast media.[1] It relies on differential variations in SSFP BOLD signal intensities between systole and diastole in myocardial territories in a manner which is dependent on the patency of the coronary artery supplying the territory (as illustrated in Fig. 1). A simple biomarker S/D, defined as the quotient of the signal intensity (segmentally averaged) at end-systole (ES) and end-diastole (ED), was previously used to identify critical coronary stenosis and affected myocardial segments in canines.[1] However, this approach does not utilize information across the cardiac cycle and relies on segmental analysis, which can degrade the specificity for detecting disease.[2]

Purpose: We evaluated the utility of Independent Component Analysis (ICA), an unsupervised pattern recognition approach, as a pixel-level ischemia detection method. Since obtaining pixel-level timeseries from real studies requires precise registration and segmentation and due to challenges in accurately identifying ischemic territories, in this study synthetic data were used. ICA performance was evaluated with respect to the number of available pixels in the myocardium, the extent of myocardial ischemia, and signal quality.

Methods: A synthetic generator of CP-BOLD timeseries: A dictionary learning approach[3] was used to create synthetic data on the basis of available real data. Flow and motion compensated 2D short-axis CP-BOLD[4] were acquired along the mid ventricle in 10 canines at baseline and under severe stenosis (>90% LAD occlusion) using a 1.5T MRI system (Espree, Siemens Healthcare). Scan parameters were: spatial resolution=1.2x1.2x8mm^4; flip-angle=70°; and T_R/T_E =6.2/3.1ms. The myocardium of each image was segmented in 24 radially consecutive segments and for each segment the average pixel intensity was recorded. Based on late enhancement imaging, segments and the corresponding segmental signal timeseries of each canine were characterized as healthy (baseline or remote) or ischemic. The timeseries were aligned such that in all subjects the ES occurs at the 10th time point and spline interpolated to length=28. All data (all studies, subjects, and segments) were arranged columnwise in a dataset 28x480, of 80 ischemic and 400 healthy timeseries. Using this dataset, two models were learned relying on dictionary-driven sparse decomposition, where each timeseries was modelled as a linear combination of patterns learned from the data. Thus, on request synthetic timeseries can be created according to the models. Using these models by design, datasets Y (of dimension 28xN) were created containing a known number of synthetic (N_I) ischemic and N-N_I healthy timeseries, respectively, thus having an **IE = N_I / N**.[2] IE reflects the extent of ischemia (ie., the percentage of pixels in the myocardium affected). We denoted the vector that contains the known originating status as **GT**. The synthetic datasets had by design the ES and ED, at the 10th and 28th time point respectively. Finally to each timeseries white Gaussian noise (with known standard deviation σ) was added, reflecting signal quality. This generator created "synthetic subject" datasets (Y) that resembled the variability of real data and reflected different acquisition related issues. ICA-based ischemia detection: Our goal was to identify, given timeseries (Y), the abnormal ones (ie., originating from an ischemic territory) with respect to the others. We used ICA[5] as time x space decomposition of Y: ie., Y=AS, where A, S were the mixing and independent component matrices, respectively. S should convey information regarding the disease status of the originating pixel and its associated timeseries. Inspired by Beckmann[5], with the Y matrix as input, we: (i) pre-processed Y with a moving average filter; (ii) pre-whittened the data projecting to the two principal components; and (iii) extracted the first row of S.[5] To detect the status of each timeseries on the basis of S we produced a binary vector by using a zero threshold on its values in order to label each timeseries as healthy or ischemic. The comparison between this vector and GT results in $\mathbf{T}^{ICA}$, the percent number of timeseries correctly identified. For a given Y we also classified each timeseries using the S/D ratio (intensity at ES divided by ED) as healthy if S/D>1, ischemic otherwise.[1] We denoted the accuracy (when compared with GT) as $\mathbf{T}^{S/D}$. Statistical analysis: Experiments included varying N, IE and σ. In each case K=100 synthetic datasets Y were generated, the analyses were repeated and we recorded $\mathbf{T}^{ICA}$ and $\mathbf{T}^{S/D}$, for each case. Differences between the collected $\mathbf{T}^{ICA}$ and $\mathbf{T}^{S/D}$ were evaluated with a paired Wilcoxon signed rank test.

Results: As Table 1 shows ICA, achieves higher accuracy than the S/D biomarker (* denotes statistical differences $p<0.05$ between ICA and S/D for the same combination of N and IE) when σ=10 (as measured in real data), across a range of N and IE. Varying added noise strength, Table 2 shows that ICA achieves higher accuracy, and overall robustness to noise (* denotes $p<0.05$). With respect to σ=0 at σ=16, ICA decreased 6% (relatively) while noise affected S/D significantly more (a relative change of 14%).

Discussion: ICA is used extensively in functional MRI (fMRI) for the detection of activation areas in the brain, by decomposing the observed fMRI timeseries in a linear combination of spatial components.[5] Drawing a parallel between fMRI and CP-BOLD, here we used ICA as a method for identifying ischemic from healthy territories on the basis of timeseries extracted from a subject's data. Unsupervised ischemia detection with ICA, evaluated with simulated data, achieves higher accuracy with respect to the S/D biomarker, which utilizes only two cardiac phases. This work relied on synthetic data, but as image acquisition improves (providing better resolution) and as the accuracy of myocardial non-linear registration algorithms increases, the proposed method can be tested and evaluated with real experimental data and in the clinic.

Conclusions: This work is the first to consider a method adapted from fMRI for characterizing and identifying ischemia with CP-BOLD MRI at rest. Using synthetic data, which allow controlling the number of pixels in the myocardium and noise (both related to imaging resolution and acquisition time), its capabilities can be tested. This proof of concept study showed that given extracted timeseries, classical unsupervised methods could be used to identify ischemic areas with CP-BOLD MRI at rest. This will enable pixel-level discrimination of disease via visualization maps of ischemia likelihood with a single MRI scan, as Fig. 2 shows. Our findings here demonstrate also the benefits of method transfer from brain fMRI, which may accelerate the adoption of this contrast and stress-free CP-BOLD imaging approach for pixel-level determination of myocardial ischemia.

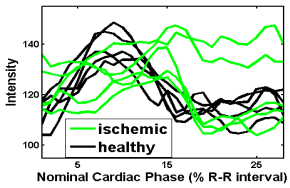

Fig. 1. Example of timeseries extracted from a canine.

Table 1. T^{ICA} and $T^{S/D}$ accuracy (mean±std) with variable N and IE.

	N=600		N=300		N=150		N=24	
IE	**ICA**	**S/D**	**ICA**	**S/D**	**ICA**	**S/D**	**ICA**	**S/D**
40%	93±3*	73±6	93±5*	73±6	91±5*	73±8	85±7*	68±12
33%	89±4*	76±5	88±5*	75±6	87±6*	74±7	82±7*	72±12
25%	82±5*	78±6	80±5*	78±7	79±6	76±7	77±8	75±12

σ	0	6	10	16
ICA	92±4*	91±4*	89±4*	86±4*
S/D	81±4	79±4	76±5	70±6

Table 2. T^{ICA} and $T^{S/D}$ accuracy (mean±std) as a function of noise strength (**σ**); N=600 and IE=33%.

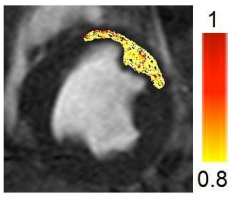

Fig. 2. A synthetic example of ischemia likelihood visualization obtained with ICA.

References: (1) Tsaftaris et al., *Circ Cardiovasc Img* 6(2):311-9 2013; (2) Tsaftaris et al., *JMRI 35(6):1338-48* 2012; (3) Rusu, Dumitrescu, Tsaftaris, *IEEE SPL*, 21(1): 6-9 2014; (4) Zhou et al., *JMRI* 31(4):863-71 2010; (5) Beckmann, Smith., *IEEE Trans. Med. Imag* 23(2):137-52 2004;