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Computers in Biology and Medicine 31 (2001) 133–142

Computers in Biology and Medicine

www.elsevier.com/locate/compbiomed

Temporal covariance analysis of first-pass contrast-enhanced myocardial magnetic resonance images ☆

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Received 24 February 2000; accepted 25 September 2000

Abstract

In this paper a temporal covariance method designed to analyze a Magnetic resonance (MR) image sequence of myocardial perfusion is presented. This method is used to map the first-pass transit of a contrast agent (Gd–chelates) through the heart. A map of bolus transit delay is constructed pixel by pixel corresponding to a myocardial reference using a temporal covariance measure. The resulting covariance map is a parametric image representing regions with different temporal dynamics. The proposed method is evaluated in 14 patients with coronary artery disease and eight healthy volunteers. Under rest and stress, covariance method is able to reveal a perfusion defect in stenosed coronary-artery-related myocardium. Furthermore, the method presents the advantage of its easy implementation and real-time parametric map construction.

Keywords: Magnetic resonance imaging; Myocardial perfusion; Time-series analysis; Covariance function

1. Introduction

Magnetic resonance (MR) imaging is a non-invasive modality that permits acquisition of high-resolution images in virtually any tomographic plane useful for anatomic and functional

☆ This work was presented at the Sixth Annual Meeting of the Society of Magnetic Resonance, Sydney, Australia, 1998.

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0010-4825/01/$ - see front matter
PII: S0010-4825(00)00028-7

evaluation of the heart [1]. The recent advances in MR imaging such as in the improvement in pulse sequences and time resolution have made this technique feasible to use contrast agent (CA) for studying heart tissue perfusion [2–6]. The most widely CA's are extracellular agents such as gadolinium chelates (Gd–chelates). This CA, in concert with rapid MR imaging, offers the potential of the first-pass myocardial perfusion imaging. Thus, Gd–chelates has been used to assess myocardial perfusion in patients with ischemic heart disease at rest [3] and during pharmacological stress [7,8]. Since, the Gd–chelates concentration influences the changes in the MR image intensity, tissue perfusion can be studied by the temporal series of MR images taken before the CA has been uniformly diluted in the whole blood volume of the body. The analysis of such series of MR images may be performed by simply observing the images or by visual evaluation of differences from image to image to obtain qualitative information about the tissue perfusion. This operation is tedious and suffers from observer bias. Furthermore, a sequence of images contains also spatially differentiated quantitative information describing the behavior of the imaged structure which is difficult to extract by visual evaluation. As an alternative to visual evaluation, information can be obtained from an image sequence using parametric analysis method. In this technique, all time curves corresponding to pixels or regions of interest, are analyzed and, assuming that curves have similar properties, certain parameters such as maximum intensity or slope curve are chosen. Thus, the image sequence is reduced to one image, called parametric image, where each pixel value is set equal to the value of the parameter at that point. In MR studies of myocardial perfusion, the method of parametric imaging has been used by Jerosch-Herold and Wilke [9]. The analysis is performed using pixel-by-pixel analysis of signal–time courses. The signal intensity curve of each pixel is smoothed by computing a least-squares constrained spline approximation. The resulting parametric image displays the maximum up-slope during CA wash-in [9]. This analysis is more reliable than the visual one. However, the determination of perfusion parameters performed for each pixel location is based on a set of heuristic rules [9]. For example, the fit to a signal–time curves is only carried out, if the standard deviation of data points acquired after the appearance of the CA in the blood pool is more than three times the standard deviation for the portion of signal–time curve before the appearance of the CA in the blood pool. This set of heuristics cuts down drastically on the number of pixel locations at which the model analysis is applied [9]. In this paper, temporal matching method to analyze MR first-pass images is proposed. Compared to parametric analysis, this technique does not assume that all intensity curves have the same general pattern across the image. In fact, images may have pixels that do not share the same characteristics in the time domain and therefore will have dissimilar dynamic intensity curves. The proposed method consists in calculating the similarity measure (temporal match) between intensity curves and a fixed reference. The generated result of this analysis is a similarity map where the value of each pixel measures its temporal similarity to the reference. This method acts as a segmentation tool, segmenting an image into regions with the same temporal properties. Using a technique based on the measurement of similarity, background noise or contrast signal originating from superposition of unwanted cardiac structures can be better removed. We have previously shown that temporal covariance technique can be used to analyze functional images of the heart [10,11]. The similarity technique is illustrated in application to MR images of 14 coronary artery disease (CAD) patients and eight healthy volunteers for the evaluation of myocardial perfusion abnormalities using Gd–chelates as a perfusion agent before and after dipyridamole infusion.

2. Method

Template matching is the process of locating an object called template within the image field. This process essentially involves sliding the template over the image field so as to arrive at the best match between the template and window or point in the search area over which the template is placed. If the template matches between an unknown object and if it is sufficiently close, the unknown object is labeled as the template object. This problem is encountered in a wide spectrum of applications from image processing of remotely sensed imagery to medical diagnosis, from computer vision to robotics. For dynamic analysis, template matching may be viewed as a temporal one. Thus, the template may be a reference time curve of a region of interest (ROI) of the myocardium or the whole left ventricle. To determine the degree of temporal match between the time sequence of images and the template a similarity measure is required. The similarity may be performed by several similarity functions such as the cross-correlation [10–13], the sum of absolute valued difference (SAVD) [14], the covariance function [15], the Tanimoto coefficient [16] and the stochastic sign change (SSC) criterion [17]. The SSC criterion and the SAVD are computationally less time consuming than the correlation coefficient. A comparison of these similarity measures to register a template in a sequence of near-infrared eye images was performed by Wagner and Galiana [18]. In this work covariance function is chosen as a similarity measure. This function has given good results in nuclear cardiac images analysis [11]. Compared to nuclear cardiac images [11], in the present study, prior to covariance analysis, images are registered and pixel time curves are normalized.

2.1. Registration

The MR image series will have constant morphology of the imaged cardiac structures, but the corresponding image intensity values will change from one image to another depending on the local pharmacokinetics of the CA. The generation of myocardial perfusion map requires the correction of some diaphragm motion, rotation and deformation of the heart. All first-pass images need to be brought into registration such that corresponding image features in myocardium overlap [9]. The similarity map should preserve the spatial resolution of the original MR first-pass images.

2.2. Normalization

All the signal intensity (SI) time curves are considered equally important. Normalization is performed to make magnitude-related feature relatively independent of any particular signal levels [19]. The aim is also not to distort the SI curves shape. Let us denote by $\mathrm{SI}(i,j,t)$ $(t=1,\ldots,T)$, the SI time curve of the (i,j)th pixel, where T is the number of images in the series:

$$X(i,j,t)=\frac{\mathrm{SI}(i,j,t)}{\sum_{t=1}^{T}\mathrm{SI}(i,j,t)}. \tag{1}$$

This scaling implies that the area under each curve is equal to 1.

2.3. Template

The reference series, $R(t)$, is chosen from the image and can be a curve corresponding either to subregion of the image or only to one particular pixel. $R(t)$ may also be a mathematical model. The reference is defined as follows:

$$R(t) = \frac{1}{M} \sum_{(i,j)\in \mathrm{ROI}} X(i,j,t), \tag{2}$$

where M is the total number of pixels in the ROI. An advantage of using a set of pixels (ROI), as opposed to a pixel, is a diminishing of noise effects because of the averaging process.

2.4. Similarity measure

The covariance value of the (i,j)th pixel is given by

$$\mathrm{Cov}(i,j) = \frac{1}{T} \sum_{t=1}^{T} (X(i,j,t) - \mu_X(i,j))(R(t) - \mu_{\mathrm{R}}), \tag{3}$$

$$\mu_{\mathrm{R}} = \frac{1}{T} \sum_{t=1}^{T} R(t), \tag{4}$$

$$\mu_X(i,j) = \frac{1}{T} \sum_{t=1}^{T} X(i,j,t), \tag{5}$$

where μ_{R} is the mean value of the reference series and $\mu_X(i,j)$ the mean value of the time activity curve of the (i,j)th pixel. The method is based on the computation, pixel by pixel, of the covariance $\mathrm{Cov}(i,j)$ between two time series representing the SI time curve of any pixel and a reference time series. The generated similarity map is an image where the value of each pixel represents the degree of temporal similarity to the reference. This similarity measure is less than $\sigma_X \sigma_{\mathrm{R}}$ in absolute value where σ_X and σ_{R} are the standard deviations of the SI time curve and the reference, respectively. A positive value of the covariance indicates that the SI time curve and the reference variables vary in the same sense while a negative value indicates that these two variables vary in opposite sense. It is important to keep in mind that all the pixels that match or mismatch the reference are equally important to describe or to interpret the information contained in the image series.

3. Results

The similarity method is evaluated on MR imaging studies from 14 CAD patients and eight healthy volunteers. Following intravenous bolus injection of Gd–DTPA-BMA (0.03 mmol/kg), sequential EKG-trigged images are obtained under breath-hold conditions using a 1.5 T whole body magnet (MAGNETON SP63, SIEMENS). A fast gradient recalled echo sequence (Turbo-FLASH) is prefaced by a nonselective 180° inversion pulse to sensitize the image contrast to T1 relaxation time (TR = 6.5 ms, TE = 3 ms, TI = 300 ms, Flip angle = 11°, FOV = 350 mm, matrix size = 128×128).

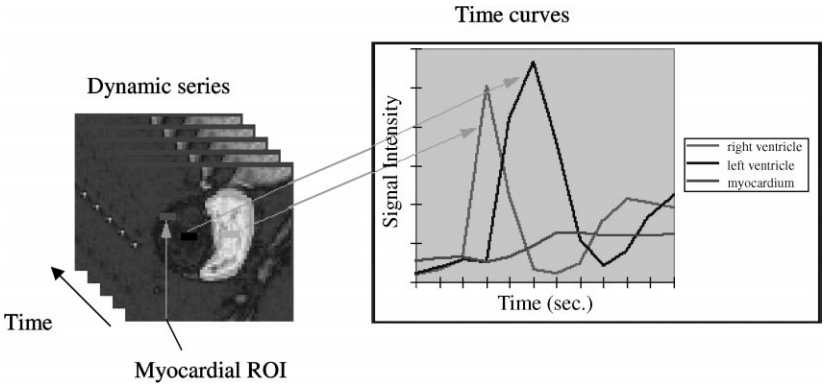

Fig. 1. Study of a patient (volunteer). References curves in blood (left and right ventricles) and myocardium.

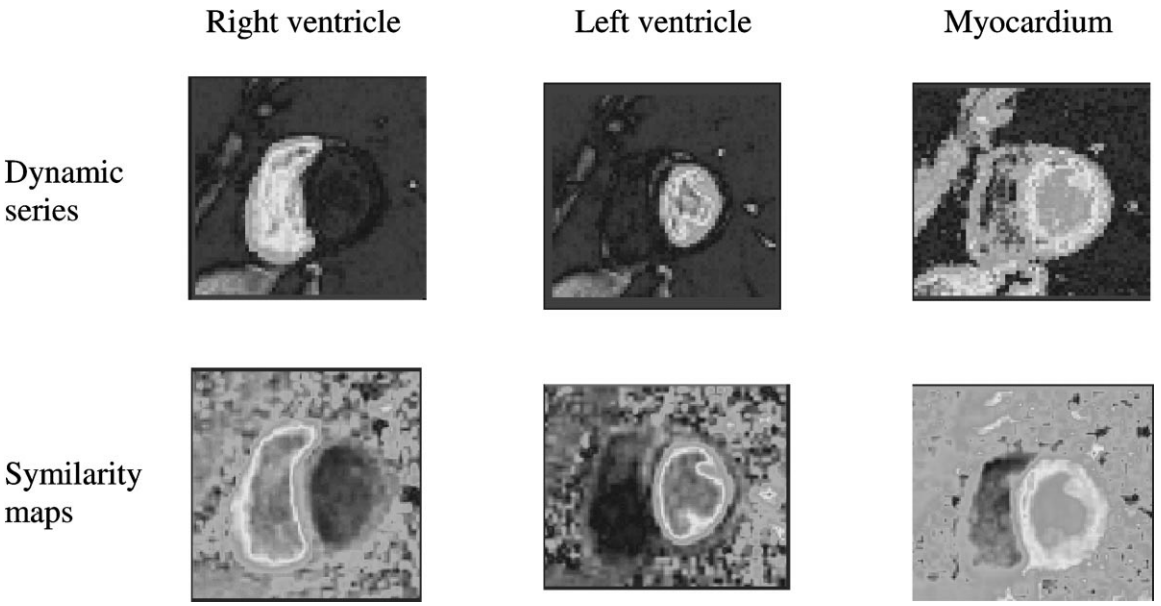

Fig. 2. Study of normal patient (volunteer). Raw data at peaks and corresponding similarity maps.

For each patient, a first acquisition is performed at rest during bolus injection of the CA and a second one is repeated 8–10 min later, without removing the patient from the magnet, under intravenous dipyridamole infusion (0.52 mg/kg) during a second bolus injection. Once the images are registered and SI time curves normalized, a reference constructed pixel by pixel is chosen. Three typical references corresponding to the left ventricle, right ventricle and myocardium are illustrated in Fig. 1. Each curve represents the first-pass transit profile of the injected CA. Fig. 2 shows the first passage of the CA, which is clearly visible, through the cardiac cavities and the corresponding covariance maps. An examination of these maps shows that the covariance method works as a segmentation tool, segmenting cardiac image into regions with the same temporal properties. Fig. 3 shows the

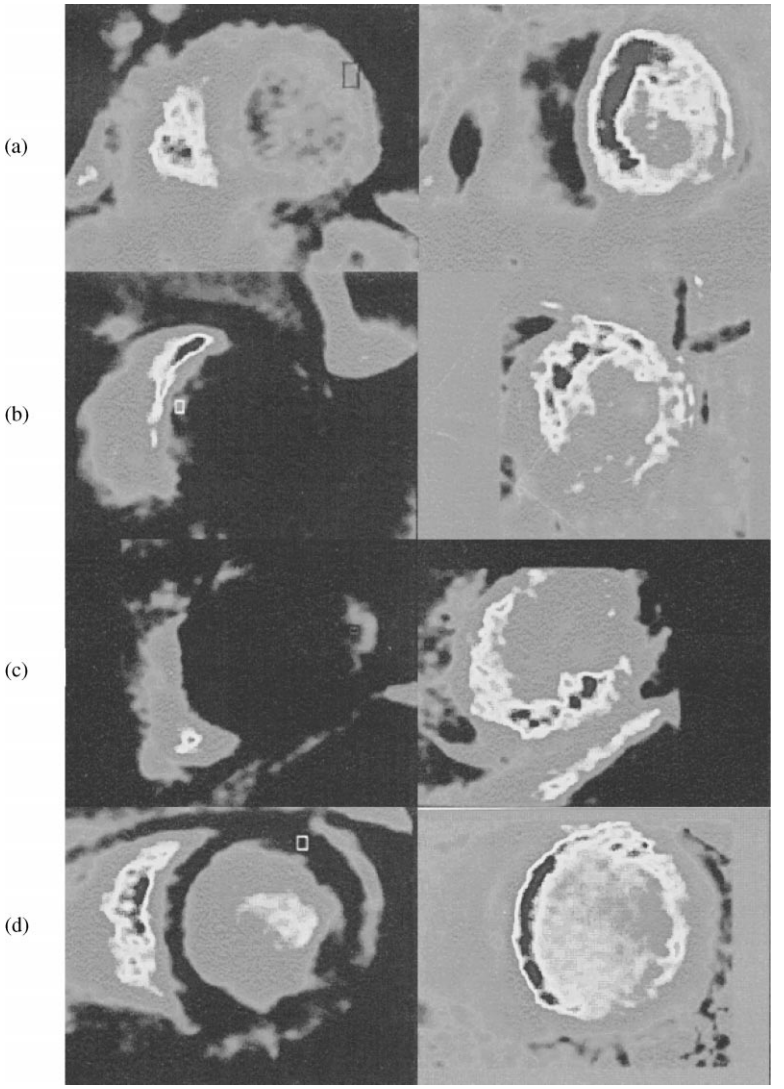

Fig. 3. Study of four pathological cases (from top to bottom: patients 4,7,3,10). The left and the right columns represent the first image of the MR sequence and the corresponding covariance map of the series, respectively.

results obtained in four CAD patients (from top to bottom: patients 4, 7, 3 and 10). The left and the right columns represent the first image of the MR sequence and the corresponding covariance map of the series, respectively. These results are obtained with the reference placed on the myocardium for the four patients (Fig. 3). In patient 4, the similarity map shows the infero and infero-lateral portions of the myocardium with delayed temporal response compared to the remaining portions of the myocardium (Fig. 3a). In patient 7, a perfusion defect in the infero-septal and lateral walls is well demonstrated at stress (Fig. 3b). Note that the defect is more pronounced in the inferior wall. The covariance method evidences a defect in the anterior and the anterior–lateral walls in patient

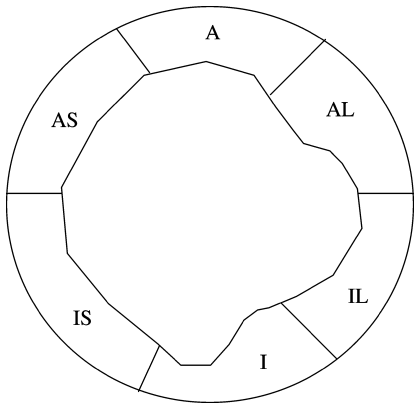

Fig. 4. Short axis view of the heart and representative regions of interest of myocardium (A: anterior wall, AL: antero-lateral wall, IL: infero-lateral wall, I: inferior wall, IS: infero-septal wall, AS: antero-septal wall).

Table 1
Statistical results

Patients	Number	Mean	SD	p
CAD (rest)	14	190.0	1.9	< 0.0004
CAD (stress)	14	192.7	1.4	< 0.0042
Control (rest)	8	202.1	2.2	

3 (Fig. 3c). A perfusion defect is illustrated in the interior wall of patient 10 (Fig. 3d) but less pronounced as in patient 7.

For statistical analysis, each generated similarity map is divided into six regions of interest corresponding to the anatomical regions of anterior wall (A), anterior-septal wall (AS), infero-septal wall (IS), inferior wall (I), infero-lateral wall (IL) and antero-septal wall (AS) (Fig. 4). The 10% truncated mean and the coefficient of variation (CV) of each sector are calculated. Truncated means are then compared in controls and patients (rest and stress) compared by ANOVA and Scheffe's test. Homogeneous similarity maps of the myocardium were obtained in control subjects as well as in patients at rest ($CV = 0.062$). In sector corresponding to abnormal perfusion, defect is evident on myocardial maps calculated from stress images. Statistical results are summarized in Table 1.

4. Discussion

To improve the diagnostic utility of MR first-pass perfusion imaging in clinical setting, a method to generate functional myocardial perfusion maps is proposed. Similarity map may be compared to the bull's eye method used in nuclear medicine but preserve the superior spatial resolution offered by MR imaging to resolve epi to endocardial flow changes. Unlike cerebral perfusion or nuclear cardiac images [11], prior generating myocardial perfusion maps, a registration procedure is required. Indeed, most patients are not able to correctly hold their breath for the acquisition duration, usually superior to 30 s, correction for respiratory motion is necessary. Manual translation is applied on

image-by-image basis and the realignment goodness is visually checked using a cine loop procedure. This visual correction does not use an objective criterion to assess its completeness. Furthermore, plane rotation of the heart has not been corrected. Thus, to overcome these problems an automated registration which corrects both the translation and rotation effects is necessary. Once the images are spatially registered, the SI curves are normalized. All the SI curves are considered equally important. Normalization is essential to make magnitude-related feature relatively independent of any particular signal levels. Note that normalization is also used in techniques like principal components analysis [20]. However, the disadvantage of the normalization is the risk of giving too much weight to SI time curves that do not contain significant information. For each MR perfusion imaging sequence, signal versus time reference is generated for user-defined ROI in the myocardium (Fig. 1). To this ROI, corresponds a reference series of mean of pixel values averaged over this ROI. The first image of the MR sequence is used to position reference ROI. The position of the ROI is adjusted to match the same anatomical region. If the resulting curve does not correspond to a myocardial transit profile, as shown in Fig. 1, different myocardial positions are tested to obtain a reference curve which pattern matches, as possible, that of a myocardial signal. Out of the patients sequence analyzed, for one patient we have not found a correct reference. Selection of an adequate reference largely depends on the registration procedure and on sufficient number of images of the series which changes from patient to patient. Thus, an automatic selection of the reference without visual inspection is very critical. The temporal covariance involves calculating the similarity between the SI curves and the chosen reference (Fig. 1). Similarity map derived from MR-registered time sequence of images allows the dynamic behavior to be depicted on a single image (map). The map result is a segmentation of the time sequences into regions that have the same dynamic properties (perfusion). Once a covariance map is calculated, its values are mapped into 0–255. The map is displayed with a 256 color look-up table and a color-coded image represents the distribution of the temporal degree of similarity to be assessed. Thus, in a map region having the same temporal evolution, the pixels have the same color (Fig. 3). For example, regions with temporal evolution matches that of the reference appear in red (Figs. 2 and 3). Regions with a maximum of delay, compared to the reference, are displayed in blue color. The aim of visual analysis is to define the presence of a perfusion defect by comparing the rest (used as reference) and stress in myocardial territories. Two observers, blinded to clinical data, determine the perfusion status using coronary angiography images. The processing of 14 pathological patients has shown that under dipyridamole stimulation (stress), covariance method is able to reveal the ischemic areas. The obtained results (Table 1) show that mean similarity values are significantly higher for controls compared to patients at rest ($p < 0.0004$) and stress ($p < 0.0042$). In normal volunteers ($n = 8$) and CAD patients ($n = 14$) at rest, our method gives a homogeneous myocardial image (Fig. 3c). In CAD patients ($n = 14$) studied under dipyridamole, a defect of perfusion is observed in the myocardium (Fig. 3d). There is in agreement between covariance technique and visual analysis.

The obtained results show that covariance method is able to detect perfusion defects in myocardial territories under rest and pharmacological stress. In the present work, the study is limited to detect the presence of a defect and not the degree of this defect. Indeed, a careful examination of the covariance maps of patients 7 and 10 shows that in both cases the perfusion defect is evidenced in inferior walls but in patient 7 it is more pronounced than in patient 10. There are several limitations in our study. First, we have not computed a perfusion index and no comparison is performed with traditional techniques (e.g. microspheres, etc.). However, our primary purpose is to apply a new method to

map the first-pass transit of CA to detect a perfusion defect. Second, we have not studied the effect of increasing or decreasing CA doses on covariance map results. Thus, it would be interesting to see the influence of CA doses on the sensitivity of the method. Third, even the obtained results in 14 patients are in good agreement with the coronary angiographic evaluation, heart motion correction must be well performed. Finally, a minimum number of images of MR sequence, corresponding to a complete myocardial profile, is required to perform a correct covariance analysis.

5. Summary

A new technique is proposed to map the first-pass transit of Gd–chelates through the myocardium. This intensity post-processing method is useful for rapid and objective evaluation of contrast-enhanced MR images. This method depends on the choice of reference region which in turn depends on the registration process. This could be improved by an adequate heart motion correction and fully automated placement of reference region. Clinical trials in larger patient population and comparative studies to nuclear medicine are needed for the further acceptance of MR myocardial perfusion imaging in the management of patients with CAD. The covariance method based on a simple mathematical model (the covariance measure) is understandable by any user; it is very fast and easy to implement on clinical scanner.

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