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Three-dimensional quantification of regional left-ventricular dyssynchrony by magnetic resonance imaging

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Abstract— **Heart failure accounts for over five million patients in the United States alone. Many of them present dyssynchronous left ventricular (LV) contraction, whose treatment by cardiac resynchronization therapy (CRT) is until now guided by electrocardiographic analysis. One third of the selected patients, however, does not respond to the therapy. Aiming at improving the response rate, recent studies showed the importance of left bundle branch block (LBBB) configurations. Therefore, in order to detect motion patterns that relate to LBBB, this paper presents a novel method for three-dimensional quantification of regional LV mechanical dyssynchrony. LV wall-motion analysis is performed on magnetic resonance imaging (MRI) cines segmented by commercial software. Mutual delays between endocardial wall motion in different LV regions are estimated by cross correlation followed by phase difference analysis in frequency domain, achieving unlimited time resolution. Rather than focusing on the systolic phase, the full cardiac cycle is used to estimate the contraction timing. The method was successfully validated against MRI tagging in five dogs before and after LBBB induction. Preliminary validation in humans with 10 LBBB patients and 7 healthy subjects showed the method feasibility and reproducibility, with sensitivity and specificity in LBBB detection equal to 95.1% and 99.4%, respectively.**

I. INTRODUCTION

Heart failure accounts for over five million patients in the United States alone, with an incidence of over 660 thousand cases every year [1]. Approximately one third of these patients suffers from a conduction system defect [2], which is typically characterized by prolongation of the electrocardiographic QRS complex beyond 130 ms [3]. The presence of a conduction system defect, such as a block, produces dyssynchronous mechanical movements of the left ventricle (LV), resulting in reduced cardiac efficiency and ejection fraction, with progressive LV dilatation and deterioration of the LV function [4].

Cardiac resynchronization therapy (CRT) is an established therapy for patients with symptomatic heart failure and ventricular dyssynchrony, able to increase long therm survival and improve heart function and quality of life [3]. Nevertheless, not all patients respond to CRT. Symptomatic improvement is achieved in approximately 70% of patients, while LV reverse remodeling is appreciated in slightly over 50% of patients [5].

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The reasons for the partial response to CRT seem to be ascribed to the limited prognostic value of QRS prolongation for appropriate selection of patients referred for CRT. In the effort to find additional means for accurate prediction of CRT response, recent studies evidenced the important role played by left bundle brunch block (LBBB) patterns in the electrocardiogram [6]. Imaging techniques can therefore become essential tools supporting accurate detection and correct analysis of these patterns.

Several imaging techniques are available that permit the assessment of mechanical dyssynchrony associated to LBBB. The time evolution of myocardial strain can be assessed by ultrasound or magnetic-resonance strain imaging. Especially magnetic resonance imaging (MRI) is able to provide accurate strain quantification by tagging techniques [7]. However, MRI tagging requires extensive computation and can be affected by reduced wall thickening and tag decay. Tissue-Doppler imaging (TDI) is an alternative echographic technique for detection of tissue velocity, which has also been tested in the context of CRT patient selection with promising results [8]. However, TDI is limited by the acoustic windows through the ribs and the intrinsic anisotropic sensitivity of the method in the longitudinal and lateral direction.

This article proposes a novel method for the analysis of LBBB patterns associated with intraventricular mechanical dyssynchrony. The method requires the acquisition of cardiac MRI cine loops. The endocardial contours are initially tracked by software CAAS MRV 3.3.1 (Pie Medical Imaging, Maastricht, the Netherlands). A dedicated algorithm is proposed that processes the time evolution of the detected contour coordinates by cross correlation and phase analysis of endocardial time-displacement curves (TDCs) [9]. Eventually, a three-dimensional (3D) timing map is generated that permits assessing the regional movement timing and, therefore, the regional degree of wall-motion dyssynchrony. Differently from previously proposed methods [10], the proposed timing quantification is based on the entire cardiac cycle rather than on the systolic phase alone.

Validation of the method was carried out by comparison with MRI tagging in five dogs before and after LBBB induction at the Physiology Department of the Maastricht University (the Netherlands). MRI tagging data were analyzed by the SinMod method [11]. In addition, the feasibility of the proposed method was evaluated in ten LBBB patients and seven healthy subjects who received an MRI scan at the Catharina Hospital in Eindhoven (the Netherlands).

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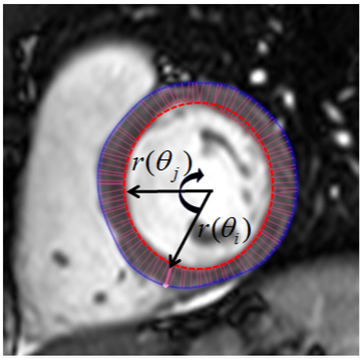

Fig. 1. Endocardial displacements evaluated at angles θ_i and θ_j.

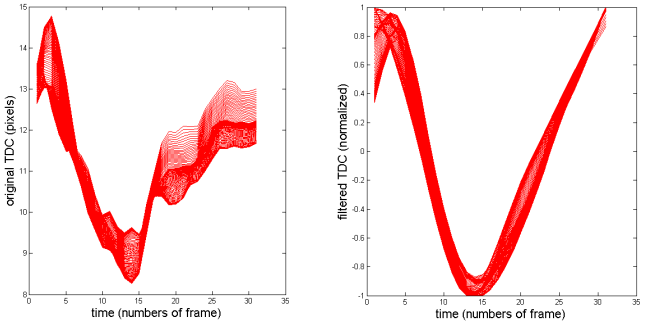

Fig. 2. (a) Original time-displacement curves. (b) Time-displacement curves after spatiotemporal filtering and normalization.

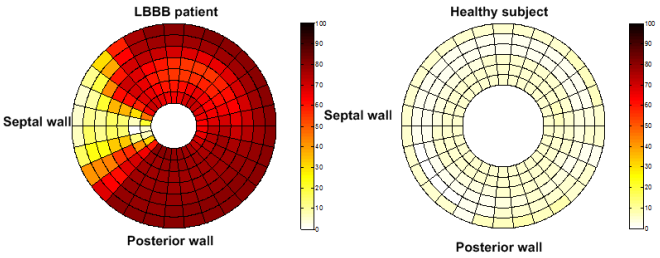

Fig. 3. Dyssynchrony estimates for an LBBB patient (a) and a healthy subject (b). Dyssynchrony is expressed as percentage of the cardiac cycle. Each ring represents a different ventricular plane from apex (inner ring) to base (outer ring).

II. METHODOLOGY

A. Acquisition

The proposed method for assessment of LV intraventricular dyssynchrony in humans is based on multislice short-axis MRI cines. These were acquired by a 1.5 T MRI scanner (Gyroscan Intera, Philips Healthcare, Best, the Netherlands) equipped with a multi-element coil. A balanced steady-state free precession sequence was used together with parallel imaging by sensitivity encoding reconstruction. Breath hold was used to avoid motion artifacts. The acquisition timing was regulated by electrocardiographic triggering. Slices of 8 mm were acquired with an image resolution of 2.2 mm. The MRI cines were exported in DICOM (Digital Imaging and Communications in Medicine) and the endocardium segmented by CAAS MRV software for magnetic resonance ventricular analysis, returning the coordinates of the endocardial wall in all slices for each time frame t_n.

B. Dyssynchrony assessment

Dyssynchrony is estimated on the basis of the mutual delays between TDCs. For each slice, based on the detected endocardial coordinates, displacement is determined as the distance between a reference point in the LV cavity and the endocardial contour [9]. Considering a radial structure originating at the selected reference point as shown in Fig. 1, the distance between the reference point and the endocardial contour is derived for all rays with an angular resolution of one degree. TDCs are derived in each slice.

Prior to the estimation of the mutual delays between TDCs, all TDCs are preprocessed by spatiotemporal filtering and normalization in order to improve the signal-to-noise ratio (SNR). Low-pass filtering in time domain is based on the assumption of smooth endocardial movements, while low-pass filtering in spatial domain is based on the assumption of continuity in the endocardial structures. Fig. 2 shows an example TDCs before and after spatiotemporal filtering and normalization.

For each slice, a reference TDC is chosen that shows the best SNR characteristics. The delay of all TDCs in the same slice with respect the selected reference TDC is then estimated. This permits deriving a relative timing for the endocardial wall in each slice. A global relative timing is then derived by estimation of the relative delays between TDCs in different slices. The delay between different TDCs can be simply estimated by determination of the peak of the cross correlation function. Different from other approaches, limited to the analysis of the systolic phase [10], the proposed approach extends the delay estimation to the entire cardiac cycle; rather than limiting to the estimation of the time to peak shortening in systole, the delay is estimated as the average delay of the entire cardiac cycle, including diastole.

The implemented cross correlation method has an implicit limitation: the time resolution is limited by the sampling period of the signals, which corresponds to the MRI-acquisition frame rate. Considering $r(\theta_i, t_n)$ and $r(\theta_j, t_n)$ to be two discrete TDCs at angles θ_i and θ_j, respectively, the time resolution of their cross correlation function is determined by the time period $t_{n+1} - t_n$. This problem can be overcome by phase spectrum analysis. After discrete Fourier transformation, the resulting TDCs in the frequency domain, $R(\theta_i, f_n)$ and $R(\theta_j, f_n)$, show a difference in the phase spectra that can be approximated with a straight line. This is due to the fact that $r(\theta_i, t_n)$ and $r(\theta_j, t_n)$ are time translations of the same curve. The delay between $r(\theta_i, t_n)$ and $r(\theta_j, t_n)$ can then be estimated as the slope $\Delta\phi$ of the phase-difference regression line without any resolution limit [9].

In general, the condition of a pure temporal translation of TDCs measured at different locations in the endocardium is not fully satisfied, and the phase difference may show poor SNR. Therefore, a least squared error estimation seems a suitable approach for the interpolation of a line to the phase-

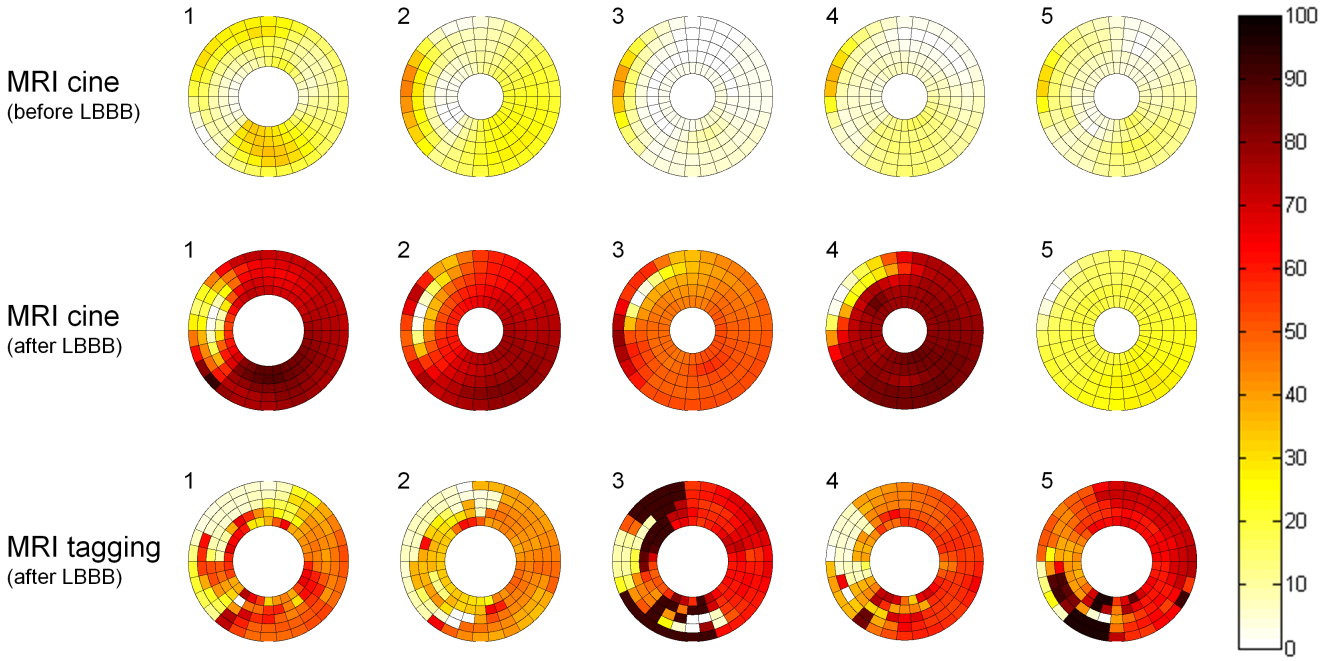

Fig. 4. Dyssynchrony estimates, represented as percentage of the cardiac cycle, by MRI cine and MRI tagging in 5 dogs before and after LBBB induction.

difference spectrum. The slope $\Delta\phi$ can then be estimated by a weighted linear regression to the phase-difference spectrum as

$$\Delta\phi = (\underline{f}^T W \underline{f})^{-1} \underline{f}^T W \left(\underline{\phi}_i - \underline{\phi}_j\right), \qquad (1)$$

with W being a diagonal matrix containing the regression weights, $\underline{f}$ being an array containing the discrete frequencies f_n, and with

$$\underline{\phi}_i = tg^{-1}\left(\frac{\Im[\underline{R}(\theta_i)]}{\Re[\underline{R}(\theta_i)]}\right),$$
$$\underline{\phi}_j = tg^{-1}\left(\frac{\Im[\underline{R}(\theta_j)]}{\Re[\underline{R}(\theta_j)]}\right).$$

$\underline{R}(\theta_i)$ and $\underline{R}(\theta_j)$ are the vectors representing $R(\theta_i, f_n)$ and $R(\theta_j, f_n)$, respectively.

At each frequency f_n, the weights for the linear regression are determined as the minimum value between the spectrum amplitudes of the two time-displacement curves [9]. As a result, higher energy components, which typically represent the endocardial movement, provide a higher contribution to the estimation of the regression line. The weight matrix W in Eq. (1) is normalized so that $\mathrm{Tr}(W) = 1$. The delay of every TDC in the LV is defined as the sum of the regional wall-motion timing computed by cross correlation and by phase spectrum analysis. Fig. 3 shows the wall-motion timing for an LBBB patient and a healthy subject. Slices from apex to base are included in the analysis. Each LV slice is segmented into 32 segments. Dyssynchrony is represented as the delay with respect to the first moving segment expressed in percentage of the cardiac cycle.

C. Validation

The method was validated at the Maastricht University, by comparison with MRI tagging in five dogs (adult mongrel) before and after LBBB induction. LBBB was induced by radio frequency ablation by use of an ablation catheter (MarinR, Medtronic Inc., Minneapolis, MN) [12]. LBBB was characterized by a wide (100 ms) QRS complex. MRI tagging was performed in five short-axis slices from LV base to mid-cavity with a temporal resolution of 15 ms.

The SinMod method was used for strain-based timing analysis in the recorded MRI tagged data [11]. This method was preferred to standard harmonic-phase analysis proposed in [7] due to more accurate displacement detection and higher robustness with respect to artifacts and noise [11]. The contraction timing was determined as the time to peak contraction. The delay with respect to the first contracting segment was associated to each segment and a quantitative plot generated (Fig. 3).

In addition to a regional dyssynchrony validation, a global indicator was also derived to obtain a correct classification between the two classes of healthy subjects and LBBB patients. The standard deviation of the detected delays along the complete LV endocardium was the adopted global indicator of dyssynchrony [9], [10].

The classification performance was also evaluated in humans, with seven LBBB patients and ten healthy subjects scanned at the Catharina Hospital in Eindhoven. The acquisition protocol in Section II-A was adopted. Classification was assessed in terms of sensitivity and specificity in LBBB detection. The threshold between the two classes (LBBB and healthy) was set at the intersection of the posterior class probabilities, assumed to be Gaussian.

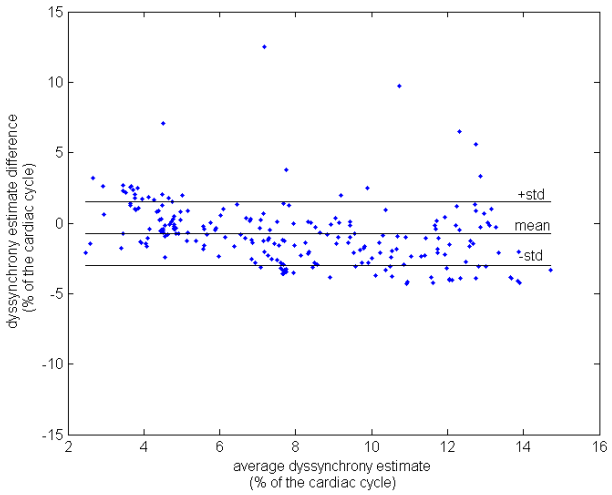

Fig. 5. Bland-Altman plot of the dyssynchrony estimate difference between two MRI scans repeated in three healthy subjects.

III. RESULTS

The agreement between the MRI tagging and MRI cine methods was assessed by comparison of the delay estimates in all 32 segments for each dog (after LBBB induction). The mean squared error (MSE) was used as measure of the distance between the estimates. The MSEs obtained for each dog were 12.78%, 12.18%, 9.48%, 10.85%, and 18.73% of the cardiac cycle, confirming a good agreement between the methods. The bias was negligible.

Two classes were defined corresponding to the dogs before and after LBBB induction. The method ability to classify the two classes was therefore evaluated. The standard deviation of the estimated delays, expressed as percentage of the cardiac cycle, was the adopted global dyssynchrony indicator. By MRI tagging, the mean standard deviations before and after LBBB were $16.7\% \pm 6.5\%$ and $19.4\% \pm 3.1\%$, respectively. By the proposed method, the mean standard deviations were $7.0\% \pm 1.9\%$ and $13.0\% \pm 6.1\%$, respectively. Student's t-test revealed a larger significance of the class separation ($p < 0.05$) by the proposed MRI cine method with respect to the MRI tagging method ($p = 0.21$). Figure 4 shows the regional intraventricular dyssynchrony estimates by the two methods in the five dogs before and after LBBB induction. With both methods, five slices from mid-cavity (inner ring) to LV base (outer ring) were analyzed.

The standard deviation of wall-motion timing in humans, estimated by the proposed method, was $17.7\% \pm 3.1\%$ and $3.1\% \pm 1.1\%$ of the cardiac cycle for the two classes of LBBB patients and healthy subjects, respectively. The mean difference was significant ($p < 0.001$). The resulting sensitivity and specificity were 95.1% and 99.4%, respectively.

Three healthy subjects underwent a second MRI scan in the same day. These data sets were then used to assess the method reproducibility. Fig. 5 shows a Bland-Altman plot comparing the contraction timing for all the corresponding segments in all subjects [13]. Mean and standard deviation are -0.72% and 2.66% of the cardiac cycle, respectively.

IV. DISCUSSION AND CONCLUSIONS

A new method is presented for 3D quantification of regional LV dyssynchrony by analysis of MRI cines. The imaging frame rate does not limit the time resolution of the estimated dyssynchrony. Comparison with MRI tagging in five dogs after LBBB induction shows good agreement. In addition, the ability of the method to produce accurate classification in dogs before and after LBBB induction was compared with MRI tagging, confirming the value of the proposed method. Promising results in terms of reproducibility and LBBB classification were also obtained in humans.

The method validation is still limited, and extensive comparison with time to peak shortening should be carried out in humans. Moreover, accurate classification of LBBB represents only a preliminary validation. The ultimate goal is the clinical use of the method for detection of LBBB patterns in relation to the prediction of CRT response. To this end, extensive dedicated validation is being planned.

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