ASSESSMENT OF CARDIAC RESYNCHRONIZATION THERAPY BY NON-INVASIVE RECONSTRUCTION OF CARDIAC ACTIVATION TIMES

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ABSTRACT
The computational reconstruction of cardiac activation times in a noninvasive manner was performed in ten patients with congestive heart failure (CHF), complete left bundle branch block (LBBB) patients undergoing cardiac resynchronization therapy (CRT) and ten patients without structural heart disease undergoing an EP study (control group). The noninvasive functional imaging technique employed in this study fused data from high-resolution ECG mapping with a model of the patient’s individual cardiac and thoracic anatomy obtained by magnetic resonance imaging. Single beat endo- and epicardial ventricular activation sequences were computed during native rhythm and ventricular pacing. A bidomain theory based algorithm was employed solving the underlying ill-posed inverse problem of electrocardiography. The control group showed a deterioration of the ventricular activation sequence during right ventricular pacing, which was found to be similar to the intrinsic activation pattern of CHF patients. CHF patients had a right-to-left septal activation with the latest activation in the epicardial lateral wall of the left ventricle. Biventricular pacing led to a resynchronization of biventricular activation sequences and to a significant decrease of the total left ventricular activation duration compared to intrinsic conduction and RV pacing (129 ± 16 versus 157 ± 28 and 173 ± 25 ms; both p < 0.05). Endocardial and epicardial ventricular activation of structurally healthy individuals and of patients with CHF or LBBB can be visualized in a noninvasive manner by the method proposed in this study. Thus noninvasive determination of individual patients’ ventricular activation properties might help to further improve positive responses to CRT by pacemaker therapy tailored to a patient’s specific needs.

KEY WORDS
Cardiac Resynchronization Therapy, Biventricular Pacing, Noninvasive Reconstruction of Cardiac Electrical Activity, Ill-posed Inverse Problem, Cardiac Activation Times

1 Introduction
Cardiac resynchronization therapy (CRT) today constitutes a well established clinical treatment procedure for patients with severe heart failure, who have not responded to optimized neurohumoral therapy. In particular, patients with wide QRS complex and severely reduced left ventricular ejection fraction (LVEF) should take advantage of CRT as demonstrated by large clinical trials [1]. Quite often a complete left bundle branch block (LBBB) in these patients can occur.

Many investigations and studies about electrophysiological and mechanical mechanisms of CRT have been performed. Little is known, however, about endocardial and epicardial activation and the related electrical activation patterns in these patients. Invasive catheter based electroanatomic mapping of ventricular activation employing, e.g., Carto (Johnson & Johnson) or EnSite (St. Jude Medical) reflects the electrical spread of excitation on right- and left ventricular endocardial sites. Information about epicardial activation, however, is strongly limited to a small area of the left ventricle, which is anatomically accessible with the catheter only via the coronary sinus. This data was acquired mainly by conventional fluoroscopy guided electrophysiological mapping as well as by electromagnetic three-dimensional non-fluoroscopic electroanatomic contact mapping techniques [2, 3], all of which are invasive procedures. In order to characterize biventricular electrical activation on both the endocardial and epicardial surfaces in heart failure patients undergoing CRT compared to the healthy control group, a reconstruction technique to estimate cardiac electrical activation times in a noninvasive manner was employed in this study.

2 Material and Methods
Computational reconstruction of electrical activation times on both the epicardial and endocardial can be performed by fusing a patient’s individual 3D geometrical information – acquired by Magnetic Resonance Imaging (MRI) – with ECG data recorded by a non-clinical standard ECG system. This data constitutes the essential input for the algorithm’s capa-
bility to solve the corresponding ill-posed inverse problem [4 – 8].

2.1 Patient population

Ten patients (1 female, mean age 63 ± 6 years, NYHA class III, LVEF < 35%) with CHF (2 patients suffered also from cardiac ischemia) and LBBB undergoing CRT and ten patients (4 females; mean age 31 ± 16 years, LVEF > 50%) without structural heart disease and normal atrio-ventricular conduction undergoing an EP study (control) were included in the study. All patients in the control group had structurally normal hearts which had been assessed by transthoracic echocardiography. The study was approved by the local ethics committee and written, informed consent was obtained from all patients.

2.2 Magnetic resonance imaging

Before the CRT-device was implanted and the electrophysiologic examination was performed, patient-specific anatomic data were obtained by MRI employing a Magnetom Vision Plus 1.5 Tesla scanner (Siemens, Erlangen, Germany). Ventricular end-diastolic geometry and torso geometry were both acquired in ECG-gated cine mode during breath-hold. The 3D-geometry of the thorax and lungs were segmented based on an MRI long axis scan, whereas the 3D-geometry of the atria and ventricles, respectively, were segmented based on an MRI short axis scan. For each patient an individual computer model including compartments of different electrical conductivities (heart, lungs, blood mass and chest surface) was constructed. For this purpose, a commercial software package (AmiraDev 3.0, TGS Template Graphics Software Inc.) was adapted for contour detection and segmentation. An exemplary result – the Volume Conductor Model (VCM) – after 3D-segmentation of the MRI stacks of a healthy patient is depicted in fig 1.

2.3 ECG mapping

A high-resolution 65-lead electrode array was applied for each patient either before intervention in the catheter laboratory (healthy control group) or after implantation of the pacemaker or defibrillator device. ECG data was recorded employing a Mark-8 system (Biosemi V.O.F., Amsterdam, Netherlands) at a sampling rate of 2,048 Hz (0.3 Hz to 400 Hz band pass filter) and an AC resolution of 500 nV/bit (16 bit AD converter, i.e., 32 mV AC input range). The Mark-8 recording system is a battery-powered (6 Volts) high-precision ECG amplifier. The related data was transferred to the recording PC via an optic fiber.

2.4 Coupling MRI with the position of electrodes

As the anatomical data was recorded based on the MRI frame, all additional geometric data had to be transformed into this frame. For this purpose seven anterior and lateral MRI markers (vitamine E-capsules were used as landmarks which were visible in the MRI stacks) and the anterior and lateral electrode positions were measured with a magnetic digitizer (FastrakTM, Polhemus Inc., Colchester, VT, USA). The electrode positions were transformed by a rigid body transformation (rotation matrix and displacement vector) minimizing the root-mean-square (RMS) distance of the seven Polhemus marker positions relative to the MRI marker positions. The posterior electrodes were directly assigned as the location of the posterior markers.

2.5 Reconstruction of cardiac electrical activation times

The computation of the ventricular activation times was performed as described in, e.g., [5, 8, 9, 10]. Briefly, the model for computing the electrical activation times is based on a quasi-static approximation of Maxwell’s equations linking the electro-magnetic behavior of the cardiac muscle to the body surface ECG. For modeling the step-like local electrical activation mimicking the depolarization sequence of the action potential of a myocyte (resting potential level: -90 mV; plateau level: 10 mV; rising time: 3 ms) at the endocardial and epicardial source points, an arctan-like function was employed. The boundary element formulation (linear triangular elements) was applied to numerically compute the relationship between the car-
diac electrical source points (on epi- and endocardia) and the potentials measured by the electrodes.

For the computation of the ventricular activation sequence the related target beats (i.e., QRS-complex of the body surface potentials in this case, where activation times of the ventricles were to be reconstructed) were selected using a semi-automated signal processing algorithm implemented in Matlab (The MathWorks Inc.). Preprocessing steps, like exclusion of corrupted channels, baseline correction and filtering were also performed in Matlab.

The functional which has to be minimized in order to solve the ill-posed inverse problem of electrocardiography is

\[ \|L\Phi - D\|_F^2 + \lambda^2 \|\Delta \tau\|^2 \rightarrow \text{min.} \tag{1} \]

with \(L\) representing the lead field matrix (relating the transmembrane potentials of the cardiac source points of the computer model to the electrode potentials), \(\Phi\) depicting the transmembrane potentials in each source node over time, matrix \(D\) representing the measured ECG signals in all electrodes over time, \(\|\cdot\|_F\) reflects the Frobenius-norm, parameter \(\lambda\) is the regularization parameter, \(\Delta\) is the surface Laplacian, and vector \(\tau\) reflects the cardiac electrical activation times in each of the source nodes. For a more detailed treatment of the optimization process the reader is referred to [5, 6]. The computation of the activation sequence \(\tau\) of a single beat can be described as follows: For one activation sequence the ECG was simulated and compared with the measured ECG. The starting vector for \(\tau\) was computed according to the critical point theorem [6]. The activation pattern was then systematically changed in an iterative manner subject to minimizing the difference between the simulated and the measured ECG data. As this functional imaging problem was ill-posed (i.e., the solution was sensitive to noise and model errors), a regularization term of the Tikhonov second-order type was included in the optimization process (second term of the functional in eq. (1)). This regularization expression (surface Laplacian effecting the activation times \(\tau\)) imposed the constraint that neighboring cardiac source points had to have similar activation times, which resulted in smooth activation patterns. Thus this type of regularization could also be regarded as spatial regularization. The influence of the amount of regularization was controlled by the parameter \(\lambda\). According to [11] the optimal value for \(\lambda\) can be found in the corner of the L-curve. The L-curve method weights the regularization amount (right term of eq. (1)) against the residual norm on (left term of eq. (1)).

The second type of regularization – regularization in the temporal domain – was achieved by approximating the shape of the action potential of a myocyte \(\phi(\tau, t)\) by an arctan-like function:

\[ \phi(\tau, t) = \frac{u}{2} \left\{ 1 + \frac{2}{a} \arctan \left[ \frac{t - \tau}{w} \right] \right\} + a. \tag{2} \]

Parameter \(a\) represents the resting transmembrane potential \((a = -90 \text{ mV in this study})\), parameter \(u\) reflects the action potential amplitude \((u = 100 \text{ mV})\) and \(w\) represents the rising time \((w = 3 \text{ ms})\). This type of regularization allowed for introducing the activation time \(\tau\) (time instant at which the resting potential level switched to the plateau level of the action potential) as the only parameter which had to be determined in the inverse computation procedure.

### 2.6 Data acquisition

For the CHF patients noninvasive determination of cardiac electrical activation was performed during native sinus rhythm (no pacing), right ventricular and biventricular pacing. Cardiac activation times for the control patients were determined during intrinsic (native) rhythm and during right ventricular pacing performed via a mapping catheter located in the right apex. Endo- as well as epicardial breakthrough sites were identified as the locations on the ventricular epi- and endocardium where depolarization could be observed first in the activation time map. The ventricular total activation duration was defined as the interval from the earliest breakthrough to the latest electrical activation of the right and left ventricle. The root mean square QRS duration was measured during native sinus rhythm and during the different pacing modes as previously described in [12] for determining the total activation duration with respect to the spread of the depolarization wavefront across the ventricles.

### 2.7 Statistical analysis

Results are shown as mean ± SD and are expressed as absolute values. Statistical analysis of the data was performed with SPSS 10.1 for Windows (SPSS Inc., Chicago, Illinois). A two-sided Students t-test (unpaired for independent samples, paired for dependent samples) was used to evaluate the results. P values < 0.05 were considered statistically significant.

### 3 Results

#### 3.1 Epi- and endocardial ventricular electrical activation of healthy subjects

The earliest ventricular activation could be observed during native sinus rhythm at an endocardial location in the right ventricular free wall. None of the patients of the control group showed a septal breakthrough at a basal-septal position in the left ventricle. Left septal activation was followed by left ventricular endocardial and right ventricular mid-septal activation. Epicardial activation could be observed in both ventricles immediately following endocardial activation.

During right ventricular pacing the ventricular activation pattern changed significantly. The activation of the left ventricle became more delayed as compared to native sinus rhythm. During right ventricular pacing, right ventricular septal activation was preceded, and the breakthrough
Ventricular activation time maps of one representative of the control group are depicted in fig. 2, the total activation times for the control group and for the CHF (LBBB) patients are given in tab. 1.

### Table 1. Differences in total activation duration (TAD) of the left (LV) and right ventricle (RV) in milliseconds in the control group and CHF (LBBB) patients during native (no stimulation) rhythm and during right (RV) and biventricular (biV) pacing. Symbols †, ‡, and †‡ represent a significant difference – i.e., a p-value of < 0.05 – in the comparisons between the corresponding different pacing procedures and rhythms, respectively.

<table>
<thead>
<tr>
<th></th>
<th>TAD LV [ms]</th>
<th>TAD RV [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>control intrinsic</td>
<td>95 ± 14*†</td>
<td>89 ± 15*†</td>
</tr>
<tr>
<td>control RV</td>
<td>125 ± 11*</td>
<td>122 ± 14*†</td>
</tr>
<tr>
<td>LBBB intrinsic</td>
<td>157 ± 28†‡</td>
<td>102 ± 19†‡</td>
</tr>
<tr>
<td>LBBB RV</td>
<td>173 ± 25‡</td>
<td>128 ± 48‡</td>
</tr>
<tr>
<td>LBBB biV</td>
<td>129 ± 16‡</td>
<td>108 ± 23‡</td>
</tr>
</tbody>
</table>

3.2 **Epi- and endocardial ventricular electrical activation of heart failure patients**

In the CHF patients, the earliest ventricular activation was also located in the right ventricular endocardium. The earliest septal breakthrough site could be localized in an apical position of the right septum in 5 patients. In the remaining patients right septal breakthrough sites were located in the mid-septal region. Due to complete LBBB left ventricular endocardial and epicardial activation was significantly delayed in each patient as compared to the control group (endocardial: 46±19 versus 17±10 ms; epicardial: 49±16 versus 10±8 ms; both p<0.01). Left septal endocardial breakthroughs were located in a mid-septal position. In all CHF patients the left ventricular activation wavefront pattern showed a high degree of similarity. It turned around the apex and spread radially across the inferior/anterior wall towards the lateral wall of the left ventricle. Ventricular activation time maps of one CHF patient for three different rhythms are depicted in fig. 3.

Right ventricular pacing showed no significant effects on septal and left ventricular activation as compared to native rhythm. The effect of right ventricular pacing on the activation of the left ventricular lateral wall was inhomogeneous in CHF patients. Some patients showed no changes whereas for others the spreading of the wavefront and the sites of latest activation shifted from (antero)lateral to (postero)lateral as compared to native sinus rhythm.

Biventricular pacing showed a relative prolongation of RV epicardial activation and a prolongation of the RV septal activation times as compared to native rhythm. During biventricular pacing the onset of LV endocardial as well as epicardial activation was significantly shortened as compared to native sinus rhythm. The earliest activation was located in the left ventricular lateral free wall on the epicardium and was followed by an endocardial breakthrough located in a right ventricular apico-septal position. The left ventricular septal breakthrough site shifted from mid-septal to apico-septal in most of the patients. Therefore, biventricular activation provoked acceleration of the electrical activation pattern and thus resulted in an improvement of ventricular synchrony. The total activation duration of the left ventricle was significantly decreased during biventricular pacing as compared to right ventricular pacing and native sinus rhythm. The total ventricular activation durations for the healthy control group...
and the CHF patients are enumerated in tab. 1.

4 Discussion and Conclusion

In the presented study a comparison between CHF patients and a control group, which consisted of individuals with structurally healthy hearts, was performed employing an algorithm determining the ventricular electrical function in a noninvasive manner. The computation was performed based on the quasi-static approximation of Maxwell’s equations. The patient’s individual volume conductor model extracted and segmented from MRI stacks was combined with high resolution ECG data in order to solve the underlying ill-posed problem [5, 8 – 10]. The novel imaging technique applied in this study enabled individual beat-to-beat electroanatomic mapping by computing the individual ventricular activation sequences.

This is to the authors’ best knowledge the first study which simultaneously investigated and evaluated endocardial as well as epicardial (b)ventricular activation during native sinus rhythm and during different ventricular pacing modes applying a novel noninvasive electroanatomical imaging method. Up to now, there has only been limited data available about the effects of different pacing modes on biventricular endocardial and epicardial activation in humans. This is mainly due to the limitations of current mapping techniques [2, 13].

Up to now considerable efforts have been undertaken to solve the inverse problem of electrocardiography to localize and image cardiac activation sequences from body surface electrocardiograms [4, 7, 14]. Nevertheless, most of these studies are either limited either with respect to clinical applicability (conducted in animals) or deliver an incomplete picture of cardiac electrical activation (e.g., visualization of epi- or pericardial activation only). Han et al., however, have been able to reconstruct electrical cardiac activation within the myocardia [4].

In this study control patients showed a deterioration of the ventricular activation sequence during right ventricular pacing which could be compared to CHF patients with complete LBBB during native sinus rhythm. During right ventricular pacing the septal, as well as the endocardial and epicardial activation times of the left ventricle, were considerably delayed compared to native sinus rhythm. The septal activation sequence changed from left-to-right during native conduction to a right-to-left septal activation pattern which could be found to be in accordance to previous data [15].

The delay between right and left ventricular endocardial and epicardial activation in CHF patients was significantly extended – compared to the control patients – which could be due to the complete LBBB. Biventricular pacing showed no influence on the direction of transseptal activation and the timing of the LV septal breakthrough, respectively, in CHF patients although the RV septal breakthrough occurred later compared to intrinsic sinus rhythm. Epicardial pacing at the left (postero)lateral wall and simultane-

Figure 3. Ventricular activation time map (numbers depict activation times of the corresponding isochrones in ms) of a representative of the CHF group. Panel (a) represents the intrinsic activation (QRS-duration: 180 ms), panel (b) the spread of activation due to right ventricular pacing (QRS-duration: 200 ms), panel (c) activation time map after biventricular pacing (QRS-duration: 178 ms). Bright areas indicate early, dark areas late activation. The ventricles are displayed in a cranial view. LV ... left ventricle, RV ... right ventricle.
ous endocardial pacing at the right ventricular apex during CRT provoked a significant decrease of left ventricular total activation duration. The activation duration of the right ventricle did not change during CRT.

There were 10 subjects/patients, respectively, in the control and CHF group in this study. Statistical conclusions on the basis of this study could not reliably be drawn. Nevertheless, most of the results were in agreement with data and findings of other (clinical) studies and as the results of this work showed, noninvasive imaging of (bi)ventricular endocardial and epicardial activation would be feasible by employing the reconstruction technique presented in this study. Noninvasive determination of cardiac electrical activation was effective for characterizing individual ventricular activation properties, especially with respect to the spread of electrical excitation within the left ventricle. This method could therefore help to further improve efficacy of CRT in terms of providing an individual with patient-specific pacemaker therapy and thus it could help increase the responder rate among CHF patients in the future.

References


