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Characteristics of inverse-computed epicardial electrograms of Brugada syndrome patients

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Abstract— **Brugada syndrome (BrS) causes sudden death in patients with structurally normal hearts. Manifestation of BrS in the ECG is dynamic and most patients do not show unequivocal signs of the syndrome during ECG screening. Electrograms (EGMs) of BrS patients show conduction delay and fractionation at the right ventricular outflow tract area (RVOT) and thus could be used for diagnosis, but their recording requires an invasive procedure. We have obtained 67-lead body surface potential mapping recordings (BSPM) of 6 BrS patients and 6 controls and computed their EGMs by solving the inverse problem of electrocardiography by using Tikhonov's regularization method. Inverse-computed EGMs presented similar activation times and durations in controls and BrS patients for apex and septum. However, RVOT EGMs showed a later activation in BrS patients than in controls (58 ± 7 vs. 39 ± 5 ms, p<0.01) and EGMs were longer (122 ± 22 vs. 85 ± 8 ms, p<0.01). Inverse-computed EGMs of BrS patients showed abnormalities consistent with those observed in electrophysiological studies and could be used for a non-invasive diagnosis and characterization of Brugada syndrome.**

I. Introduction

Brugada syndrome (BrS) is a heritable arrhythmia syndrome that causes sudden death in young adults with structurally normal heart [1]. BrS is diagnosed on the basis of the clinical and familiar history of the patient and a characteristic ECG pattern displaying a coved-type ST segment ≥ 0.2 mV in right precordial leads (referred as type I ECG) [2]. However, the clinical manifestation is often dynamic and shows variations over time, including transient normalization of the ST segment and conversion to a saddleback-type pattern [1]. Specifically, BrS patients present spontaneous type I ECGs or a saddleback-type ECG with similar probability during follow-up but about half of their ECGs may not present any abnormality [3]. Although saddleback-type ST segments are linked to BrS since they are usually found in this group of patients, they are not considered as diagnostic unless converted to a type I ECG after administration of ajmaline or flecainide [4].

Experimental studies have demonstrated that heterogeneity and conduction delay within the epicardium of the right ventricular output tract (RVOT) contribute to the ECG characteristics observed in BrS patients [5], [6]. However, the contribution of depolarization and repolarization abnormalities in the genesis of the surface ECG is still a matter of debate [7]: while some groups believe that a depolarization delay in the RVOT is the main cause of the observed ECG in BrS [8], [9] other groups support the hypothesis that it may be caused by transmural heterogeneities in the shape of action potentials in the RVOT region [10], [11]. Although these hypotheses are not completely exclusive it may be of importance to determine which is the prevalent mechanism in BrS patients in order to develop diagnostic tools which may increase the sensitivity in the diagnosis of the syndrome.

Analysis of the electrical activity by recording epicardial or endocardial electrograms (EGM) is a valuable tool for the understanding of this pathological condition. In fact, EGMs recorded in the RVOT have revealed that the electrical activation in this region is delayed and discontinuous, which is reflected in delayed and fractionated EGMs [12]. However, recording of EGMs is an invasive procedure only performed in patients already diagnosed with the syndrome. In this study, we computed EGMs from non-invasive recordings by solving the inverse problem of the electrocardiography in BrS patients. Inverse-computed EGMs of BrS patients were compared to those of control subjects in terms of their activation times and duration.

II. Methods

A. Patient Population

In this study, 6 patients diagnosed with BrS and 6 control subjects were included. The clinical diagnosis of BrS was established prior to our study and based on the presence of a coved-type S-segment elevation ≥ 0.2 mV in two right precordial leads either spontaneously or after ajmaline or flecainide administration. Selected normal subjects had no history of previous heart disease and a normal resting ECG.

B. BSPM recording

A total of 64 chest and back leads were acquired simultaneously for each subject in addition to the standard limb leads for 2 minutes. Electrodes were mounted on an

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adjustable vest [13] at locations depicted in Fig. 1. Signals were acquired at a sampling rate of 2048 Hz, with a resolution of 1 μV and a bandwidth of 500 Hz. Before acquisition, signal quality of all leads was visually inspected and ECG recordings were stored for off-line processing.

Standard ECG leads were computed from BSPM leads recorded at positions more similar to the standard ECG leads (see Fig.1).

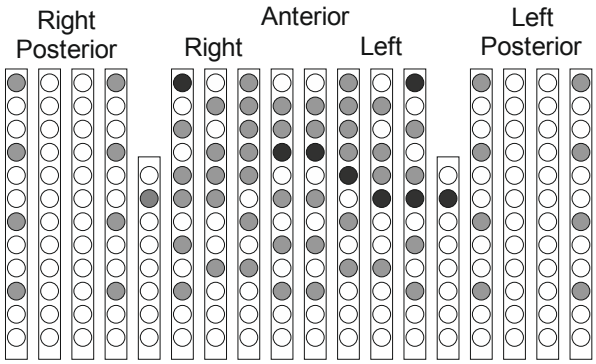

Fig. 1. Electrode position in our BSPM system. Black circles correspond to the approximate location of precordial, right and left arm leads.

C. ECG signal processing

ECG signals were processed using Matlab 7.10.0 (The Mathworks Inc, The Netherlands). First, the baseline was estimated by filtering with a butterworth 10th order low-pass filter with a cut-off frequency of 0.6 Hz after decimation to a sampling frequency of 51.2 Hz. Baseline was interpolated to 2048 Hz and subtracted to the original recording. Then, ECG signals were filtered with a 10th order, low-pass Butterworth filter with a cut-off frequency of 70 Hz. Power spectral density of all signals was computed by using a Welch periodogram with a hamming window of 8 seconds and 50% overlap. Leads presenting more than 0.5% of their spectral content at 50Hz were filtered with a 2nd order IIR notch filter centered at 50 Hz. All leads were visually inspected after filtering and leads with noticeable noise or very low amplitude were excluded from further analysis.

QRS complexes were detected by selection of local maxima after steeper slopes in a simplified ECG obtained by polyline splitting [14]. Then, averaged PQRST complexes were obtained by template matching-averaging 120 seconds of the recordings. Fiducial points in averaged beats were detected by selecting points preceding or following segments with steeper slopes in a simplified beat obtained by polyline splitting. Fiducial point detection was then manually verified. P_{onset} and T_{offset} served as anchoring points for baseline estimation on the averaged beats and the remaining baseline was subtracted.

D. Inverse problem resolution

In order to obtain the potentials on the heart surface from the potentials recorded non-invasively from the torso surface of the BrS and control subjects, we solved the inverse problem of the electrocardiography by using the Boundary Element Method (BEM) [15]. Our torso model, depicted in Fig. 2, is composed of two conductive volumes: the heart and the torso, with an isotropic and homogeneous conductivity of 0.2 S/m and 0.1 S/m respectively. Both surfaces were tessellated into flat triangles, using 4051 nodes and 7958 faces for the heart surface and 682 nodes and 1302 faces for the torso surface.

According to the BEM formulation [16], [17], potentials on the surface of the torso can be computed from potentials on the heart surface by using (1)-(3):

$$A_1 x = b \quad (1)$$

$$A_1 = \begin{pmatrix} D_{HH(nxn)} & G_{HH(nxn)} \\ D_{BH(mxn)} & G_{BH(mxn)} \end{pmatrix}, \quad x = \begin{pmatrix} \Phi_H \\ \Gamma_H \end{pmatrix}, \quad b = \begin{pmatrix} -D_{HB(nxm)}\Phi_B \\ -D_{BB(mxm)}\Phi_B \end{pmatrix} \quad (2)$$

$$\Phi_B = A\Phi_H = \left(D_{BB} - G_{BH}G_{HH}^{-1}D_{HB}\right)^{-1} \cdot \left(G_{BH}G_{HH}^{-1}D_{HH} - D_{BH}\right)\Phi_H \quad (3)$$

where Φ_H is the potential on the surface of the heart, Φ_B is the potential on the surface of the torso, Γ_H is the potential gradient of the heart, D_{XY} is the potential transfer matrix from point Y to point X and G_{XY} is the potential gradient transfer matrix from point Y to point X.

The inverse problem can be solved by computing the inverse of matrix A (A^{-1}). However, A^{-1} is ill-conditioned and, in order to overcome the ill-conditioned nature of A^{-1}, the system needs to be regularized. This regularization can be accomplished by using Tikhonov's method, which consists of a minimization problem (4):

$$\min_{x \in E^n} \left\{ \left\| A\Phi_H - \Phi_B \right\|^2 + t \left\| B\Phi_H \right\|^2 \right\} \quad (4)$$

where A is the transfer matrix, t is the regularization parameter obtained with the method of the L-curve and B is the spatial regularization matrix which is the identity matrix (zero-order). Therefore, the inverse problem can be solved by using the expression (5):

$$\Phi_H(t) = \left(A^T A + tB^T B\right)^{-1} A^T \Phi_B \quad (5)$$

Unipolar electrograms were then computed by applying (5) on the averaged beats previously computed for each electrocardiographic lead.

E. EGM measurements

Computed epicardial electrograms (EGMs) were analyzed in terms of their activation times and the duration of the QRS complex. Activation times were computed as those instants with a maximum –dV/dt. Activation time was defined as the difference between each activation time and

the earliest. Duration of QRS complexes was measured by an experienced observer on the EGM tracings.

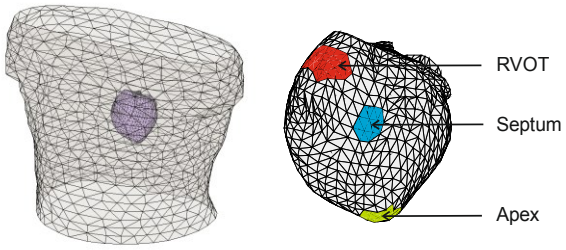

Fig. 2. Heart model used and studied epicardial regions.

F. Statistical analysis

Activation delays and durations of BrS patients and controls were compared for different regions of the heart. EGMs from septum, apex and RVOT region were analyzed (see Fig. 2) and values were given as mean ± std. Differences in measurements between BrS patients and controls were evaluated in each heart region by using an unpaired Student's t test. A p value lower than 0.01 was considered significant.

III. Results

Type I ECGs were found in the computed standard twelve-lead ECG in 3 patients (BrS-I) at the time of the BSPM recording, while 3 patients presented a non-type I ECG (BrS-nI). Computed electrograms of three subjects (control, BrS-I and BrS-nI) are depicted in Fig. 3. EGMs at the RVOT region were noticeably longer and more fractionated in BrS patients as compared to controls both for BrS-I and BrS-nI groups. EGMs computed for other regions of the epicardium presented less fractionation and shorter QRS complexes.

As depicted in Fig. 4.A, computed activation times were consistent with experimental observations, with a first depolarization of the septum, followed by the apex and a later depolarization of the RVOT, both for controls and BrS patients.

Differences in activation times between controls and BrS patients for septum (15 ± 2 vs. 17 ± 3 ms) and apex (31 ± 2 vs. 33 ± 4 ms) were not significant. However, activation delay in the RVOT region in controls vs. BrS patients differed significantly: 39 ± 5 vs. 58 ± 7 ms ($p<0.01$).

Duration of QRS complexes in the EGMs of controls vs. BrS patients did not differ significantly for septum (84 ± 13 vs. 91 ± 17 ms) or apex (79 ± 6 vs. 88 ± 10 ms), as it can be observed in Fig. 4.B. EGMs at the RVOT region of controls were significantly shorter than those of BrS patients: 85 ± 8 vs. 122 ± 22 ms ($p<0.01$).

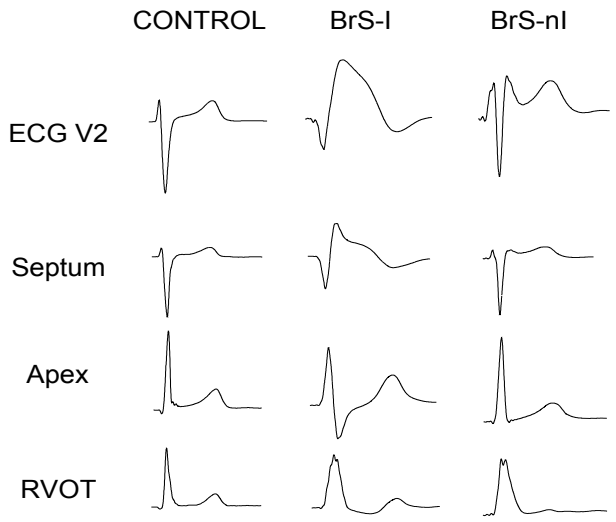

Fig. 3. Electrocardiograms and computed electrograms of controls and BrS patients from septum, apex and RVOT.

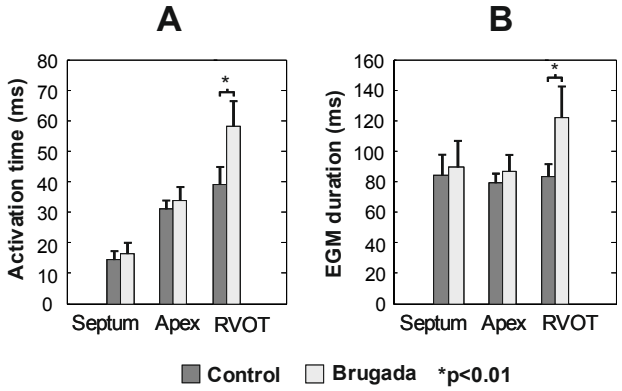

Fig. 4. Duration and activation times of EGMs in controls and BrS patients from septum, apex and RVOT.

IV. Discussion

A. Main findings

In this research, we have obtained epicardial electrograms of controls and BrS patients by solving the inverse problem of the electrocardiography. Inverse-computed EGMs of BrS patients have shown a delayed activation of the RVOT and long and fractionated EGMs in the same region. EGMs obtained for other regions of the epicardial surface did not present durations and/or activation times that differed from those obtained for control subjects.

B. Comparison with previous studies

Diagnosis of BrS patients based on the standard ECG lacks sensitivity due to the dynamic nature of ST elevation. However, analysis of BSPM maps has shown that QRS complexes of BrS patients present specific characteristics that may allow the identification of these patients even in the absence of a type I ECG [18]. Analysis of the inverse-computed electrograms of BrS patients has shown an abnormal activation in the RVOT and this suggests that this

region may be involved in these non-transient specific characteristics observed in BSPM maps of BrS patients.

Characteristics of our inverse-computed EGMs are consistent with experimental results in human healthy subjects, reflecting the expected sequence of activation and EGMs of similar duration all over the epicardium. More importantly, computed EGMs of BrS patients are also consistent with recent electrophysiological studies [12], reflecting delayed and fractionated activations in the RVOT region.

C. Limitations and future work

Although our findings are consistent with those presented in the literature, we do not have simultaneous recordings of EGMs and BSPMs which may be useful for validating our computed EGMs.

Our results suggest that inverse-computed EGMs may help in diagnosing BrS. However, a larger population of BrS patients, controls and patients with other electrophysiological disorders should be included in our study in order to elucidate the sensitivity and specificity of the EGM measurements that can be obtained.

The same torso model was used for all the patients in our study. Although variations in shape do influence the computed EGMs and thus customized torso models may allow a more accurate calculation of EGMs it may not feasible to obtain customized torso models for a large population of BrS patients. However, we believe that the proposed methodology allows comparison of the computed EGMs among different groups of patients.

V. Conclusion

Inverse-computed EGMs of BrS patients show activation abnormalities in the RVOT region, consistent with experimental observations. Analysis of EGMs computed by solving the inverse problem of the electrocardiography appears as a promising tool in the non-invasive diagnosis of the Brugada syndrome.

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