Exploring Role of Accessory Pathway Location in Wolff-Parkinson-White Syndrome in a Model of Whole Heart Electrophysiology

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Abstract

Introduction: *As the location of the accessory pathway in Wolff-Parkinson-White (WPW) may serve as a bio-marker for patient morbidity, recent clinical studies have aimed to understand the influence of location on the 12 lead electrocardiogram (ECG) used for patient diagnostics, as well as patient outcome. Furthermore, simulation studies have also been conducted to better elucidate the poorly understood mechanisms of the disease. However, clinical studies only provide limited information due to experimental and ethical limitations, and simulations studies have only been performed on simplified models. We therefore aimed to investigate the influence of the location of accessory pathways on the 12 lead ECG using a physiologically-detailed whole heart model of electrophysiology (EP) that is capable of providing in-depth information on the underlying electrical mechanisms of WPW.*

Methods: *In previous work, a physiologically-detailed model of whole heart EP had been built and personalized for a single subject to generate a realistic normal sinus rhythm. Locations of accessory pathways were automatically inserted within the electrically-isolated basal surface of the heart using universal ventricular coordinates (UVCs). For every location, cardiac sources and 12 lead ECGs were computed using an efficient cardiac simulator. 12 lead ECGs were evaluated for clinical markers of WPW. Electrical mechanisms are explored for two locations exhibiting highest and lowest morphological differences in the 12 lead ECG.*

Results: *Not all accessory pathways resulted in 12 lead ECGs exhibiting morphological markers for WPW in agreement with clinical evaluation. This may be due to the representation of the accessory pathway or inherent dynamics of WPW. Investigation into cardiac sources reveals a pre-excitation wavefront within the affected ventricles, causing retrograde activation of the His-Purkinje System, that later merges with the wave-front stemming from normal activation of the His-Purkinje System.*

1. Introduction

WPW syndrome is a common clinical disorder affecting up to 2.0% of the population leading to paroxysmal palpitations and morbidity through supraventricular tachycardias or sudden cardiac arrest [1]. The disease is classified by the presence of one or more accessory pathways allowing abnormal AV conduction outside of the normal conduction system through the AV node that connects with the His-Bundle of the ventricular His-Purkinje System. While localization of the accessory pathway using the 12 lead ECG or invasive electro-anatomical mapping is important for ablation, the location of the accessory pathway may also serve as a bio-marker for the extent of disease manifestation and morbidity, as well as ablation success.

Clinical studies have therefore been conducted to explore the influence of location of accessory pathways on the 12 lead ECG, clinically relevant ECG metrics indicative of cardiac disease, and the prognosis of patients [2]. Clinical studies are limited, however, due to ethical and experimental limitations and thus fail to offer insight into electrical phenomena. *In silico* cardiac models of EP have thus been utilized to both understand the actual mechanisms of WPW within the heart and to assist in automated localization approaches. However, previous *in silico* studies have only been performed on simplified models due to computational restrictions.

We therefore aimed to investigate the underlying electrical mechanisms of WPW and the influence of the location of accessory pathways on the 12 lead ECG using an efficient and physiologically-detailed whole heart model of EP. Locations of accessory pathways within the model were automatically sampled within the electrically-isolated basal surface using UVCs. Simulated 12 lead ECGs for each location are compared to the 12 lead ECG under healthy sinus rhythm and evaluated using clinical markers. For two locations producing the minimal and maximal morphological variation in the 12 lead ECG, electrical phenomena within the heart are detailed.

2. Methods

Within previous work, a model of ventricular EP was built from clinical magnetic resonance images and personalized according to clinically-recorded 12 lead ECGs for a single subject (male, 45 years of age) [3]. This model was extended to include a more physiologically-detailed representation of the His-Purkinje system [4]. Atrial EP was then accounted for and delayed AV conduction was allowed through an AV node located at the base of the right atrium connected to the His-Purkinje System. The right and left ventricular outflow tracts were assigned as generic tissue in the torso volume conductor. Repolarization was dictated by gradients in action potential duration within the Mitchell-Schaeffer ionic model that were implemented by assuming a linear relationship with activation as reported within experimental work [5–7]. To automatically control and alter parameters of EP, the model had been equipped with an abstract reference frame comprising both UVCs [8] and universal atrial coordinates [9]. For full details and intricacies on the model and personalization, we refer to [3, 4, 6].

2.1. Sampling Schematic

Locations of accessory pathways within the electrically-isolated basal surface of the heart were automatically sampled using UVCs [3]. Within each ventricles, the rotational coordinate was sampled 20 times through the full rotational range. Within the left and right ventricles, the rotational limits are $\pm\pi$ and $\pm\pi/2$, respectively. For each rotational value, an accessory pathway was then sampled at the endocardium ($\rho = 0$). As the ventricular outflow tracts were not considered conductive myocardium, locations within this region were removed from the sampling set. In total, 16 left-sided and 7 right-sided locations were sampled to total 23 accessory pathways.

2.2. Cardiac Simulation

Underlying cardiac sources and the 12 lead ECGs are computed for every sampled accessory pathway location in addition to normal sinus rhythm. Cardiac activation and repolarization is simulated using the reaction-Eikonal method in the mono-domain formulation without diffusion [10]. 12 lead ECGs were computed using lead field matrices [11]. The simulation framework is implemented within *CARPentry* [12] and the *openCARP* simulation environment [13].

2.3. ECG Analysis

All 12 lead ECGs were filtered using a low-pass $60\,\mathrm{Hz}$ filter in accordance with typical clinical filter settings. To account for amplitude scaling occurring in lead field projection, all signals were also scaled by 0.275. The extent of morphological variation from the 12 lead ECG under normal sinus rhythm was quantified using a L2-norm.

3. Results

UVCs could be used to automatically sample locations of accessory pathways within the electrical isolation layer of the ventricles. Highest and lowest observed losses of 0.82 and 0.45 occur in locations on the anterior side of the left ventricular near the right ventricular outflow tract and on the endocardium of the right-ventricular free wall, respectively (both indicated on Fig. 1A). Not all 12 lead ECGs exhibit features indicative of WPW. Within sites located on the right-ventricular free wall and for a site located on the posterior left-ventricular free wall normal sinus rhythm is mostly maintained.

At the location on the right-ventricular free wall, normal sinus rhythm is mostly maintained as the pre-excitation of the right ventricle progresses slowly and does not disrupt normal activation of the left ventricle (bottom panel Fig. 2). A merging of the two wave-fronts is observed and results in activation resembling normal sinus rhythm (compare $275\,\mathrm{ms}$ on bottom and top panels in Fig. 2). Although a delta wave is more present than under sinus conditions, a prolonged PR interval outside clinical markers for WPW is thus observed from this activation pattern. The expected negative deflection in V1 is however, observed due to a lack of left-ventricular activation and a right-ventricular wave-front that generates no positive signal for V1.

When the location of the accessory pathway is located on the anterior-side of the left-ventricular epicardium, as seen in the highest loss, activation of the ventricles occurs altogether earlier but in a similar pattern (center panel in Fig. 2). All common markers of WPW include a shortened PR interval, presence of a delta wave, and a QRS complex greater than $120\,\mathrm{ms}$ were observed within the 12 lead ECG in this location. Note that precordial leads V1 and V2 have a strong positive deflection resulting from more basal activation of the right ventricle from the left-ventricular septum (see $200\,\mathrm{ms}$ and $225\,\mathrm{ms}$ in center panel of Fig. 2) agreeing with clinical markers for Type A WPW. Earlier onset or inversion of the T-wave is observed as abnormal repolarization is linked to abnormal activation.

4. Discussion

Mechanisms underlying WPW were studied within a personalized and physiologically-detailed model of whole heart EP of a single subject. Locations of accessory pathways were sampled within the electrically-isolated basal surface and simulated using an efficient cardiac simulator. Data developed during this study could be used for local-

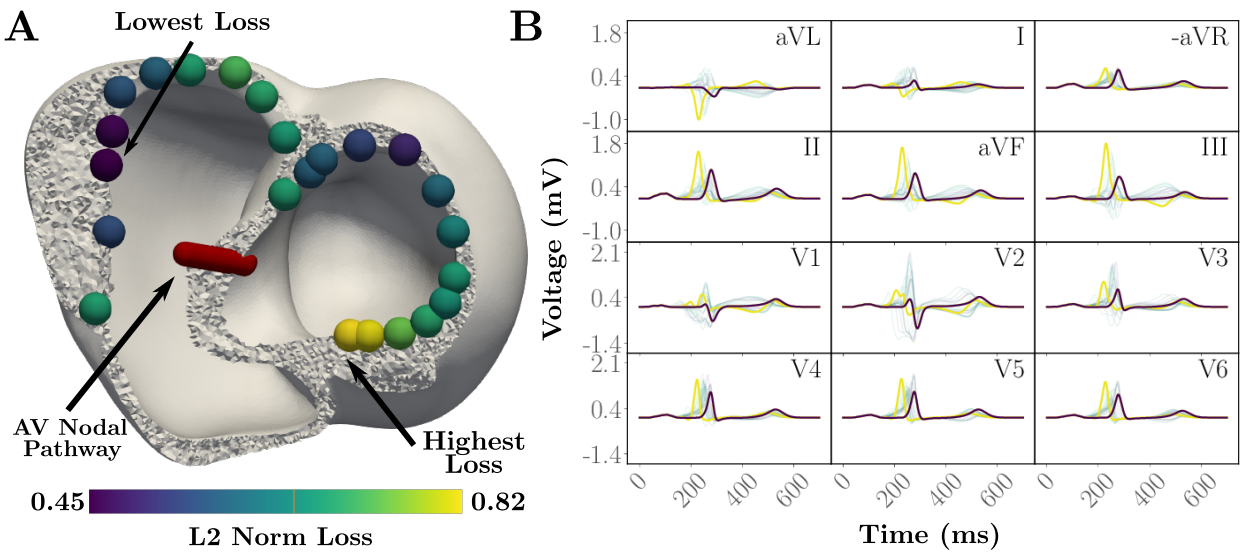

Figure 1. Locations of accessory pathways within the electrically-isolated basal surface (**A**) lead to morphological variations in the 12 lead ECG (**B**). Coloration corresponds to the L2-norm compared to the simulated 12 lead ECG under normal sinus rhythm (black). The locations with the highest and lowest observed L2-norms are indicated. Location of the AV nodal pathway is also indicated and colored in red.

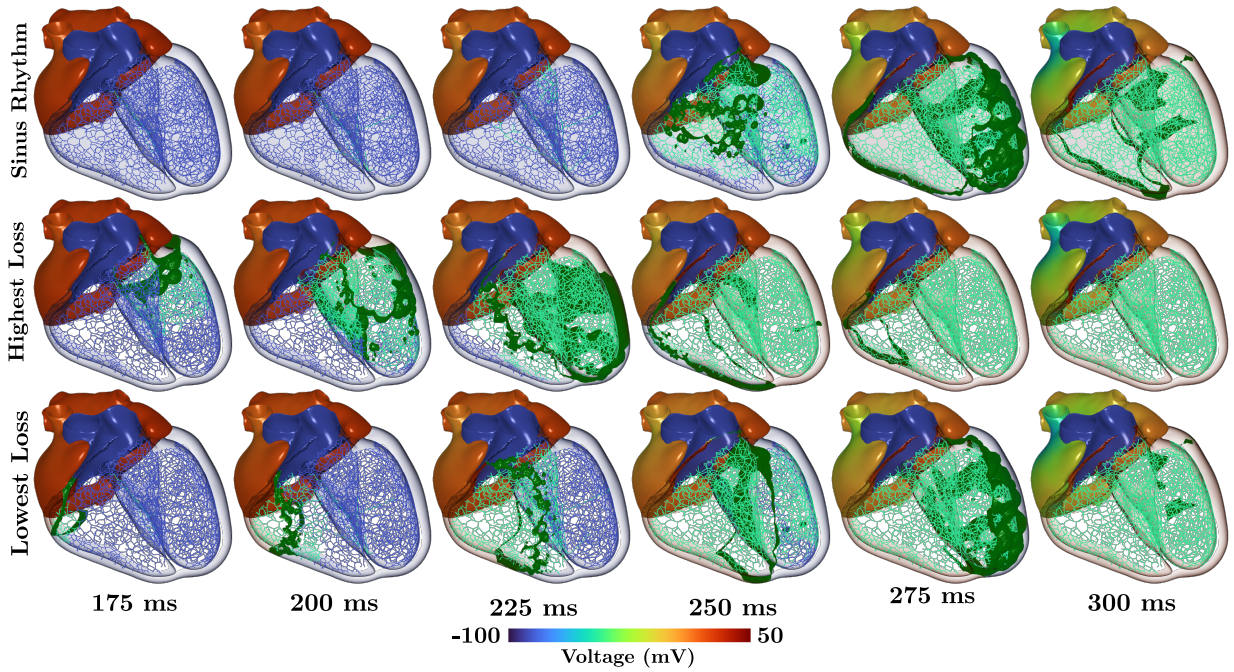

Figure 2. Trans-membrane voltage within the heart for a single accessory pathway resulting in the highest (center) and lowest (bottom) morphological differences in the 12 lead ECG in contrast to normal sinus rhythm (top). Membrane voltages for the atria are color-coded according to the color map. Green isolines in the ventricles indicate $-40\,\mathrm{mV}$.

ization algorithms when expanded to a larger model cohort capable of representing the WPW patient population.

Due to the simplicity of the model used to model accessory pathways, simulated 12 lead ECGs for sampled locations of accessory pathways (Figure 1A) did not consistently exhibit standard clinical manifestations of WPW for

the relevant type (Fig. 1B). Pathways are known to behave more similar to a Purkinje fiber of various lengths stemming from an atrial insertion point to the ventricles than a simple hole in the basal isolation. This facilitates shortened PR intervals and the onset of the delta wave, especially in accessory pathways located within the right ventricle with longer activation. To account for the multitude of influencing factors, e.g. oblique course of the accessory pathway, a more complex model of the accessory pathway is needed to gain clinical relevance.

Various other mechanisms of WPW should also be accounted for to gain clinical viability. Namely, the possibility of multiple accessory pathways was not accounted for, which may lead to more complex manifestations of WPW and the initiation of reentry-circuits. Mechanisms leading to sudden cardiac death and ventricular tachycardia within WPW were not yet explored and remain unclear. Accessory pathways should also be considered within the the right and left-ventricular outflow tracts.

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