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A Large-scale Virtual Patient Cohort to Study ECG Features of Interatrial Conduction Block

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Abstract: Interatrial conduction block refers to a disturbance in the propagation of electrical impulses in the conduction pathways between the right and the left atrium. It is a risk factor for atrial fibrillation, stroke, and premature death. Clinical diagnostic criteria comprise an increased P wave duration and biphasic P waves in lead II, III and aVF due to retrograde activation of the left atrium. Machine learning algorithms could improve the diagnosis but require a large-scale, well-controlled and balanced dataset. In silico electrocardiogram (ECG) signals, optimally obtained from a statistical shape model to cover anatomical variability, carry the potential to produce an extensive database meeting the requirements for successful machine learning application. We generated the first in silico dataset including interatrial conduction block of 9,800 simulated ECG signals based on a bi-atrial statistical shape model. Automated feature analysis was performed to evaluate P wave morphology, duration and P wave terminal force in lead V1. Increased P wave duration and P wave terminal force in lead V1 were found for models with interatrial conduction block compared to healthy models. A wide variability of P wave morphology was detected for models with interatrial conduction block. Contrary to previous assumptions, our results suggest that a biphasic P wave morphology seems to be neither necessary nor sufficient for the diagnosis of interatrial conduction block. The presented dataset is ready for a classification with machine learning algorithms and can be easily extended.

Keywords: Interatrial conduction block, interatrial block, ECG simulation, P wave, statistical shape model, bi-atrial shape model, electrophysiological simulation, 12-lead ECG

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1 Introduction

Interatrial conduction block (IAB) refers to a conduction disturbance due to block or delay in the propagation of electrical impulses from the right atrium (RA) to the left atrium (LA) via the typical interatrial pathways Bachmann's bundle (BB), upper and lower posterior bridges and via the coronary sinus. As a result, the conduction time between the atria is prolonged compared to the healthy case. IAB is not only a risk factor for atrial fibrillation, but can also lead to thromboembolism (including embolic stroke), myocardial and mesenteric ischemia, cognitive impairment, and dementia [1, 2].

IAB can be diagnosed by prolonged and biphasic P waves (duration $\geq$ 120 ms) in the 12-lead surface electrocardiogram (ECG) [1, 2] in a cheap, easy-available and non-invasive manner. Bayés de Luna et al. recently presented patients with atypical IAB in terms of morphology and duration [1] who did not fulfill the clinical diagnosis criteria. This suggests that the role of both features for the diagnosis of IAB might have been overestimated in the past. An automated analysis of P wave features with machine learning (ML) algorithms could improve the diagnosis further but requires a large, balanced and well-controlled dataset.

So far, IAB was mainly studied in vivo by analyzing ECG signals [1] in combination with activation maps derived from epicardial mapping [12]. In silico research on IAB was to the best of our knowledge so far only published by Gao et al. [4] and our group [5]. Whereas previous work in our group did not include IAB in BB but anatomical variability, Gao et al. studied IAB in BB bud did not include anatomical variability. With statistical shape models (SSMs), large-scale and well-controlled datasets with predefined IAB parameters can be generated to study IAB under consideration of the anatomical variability in the general populationd.

We present a dataset of 9,800 12-lead ECG signals (4,900 healthy, 4,900 IAB) based on a bi-atrial SSM [7] and the fast marching (FaMaS) method [11] coupled to a torso model to study ECG features of complete IAB in BB. An automated feature analysis was performed to investigate P wave duration, morphology and P wave terminal force in lead V1 (PTF-V1) in healthy models and models with IAB.

2 Methods

2.1 Generation of the ECG Dataset

2.1.1 Virtual Cohort Generation

We used 98 pre-existing atrial geometries derived from the bi-atrial statistical shape model developed by our group [7]. All geometries are publicly available [6] and are set up with interatrial bridges, fiber orientation and tags for anatomical structures. The coefficients of the eigenvectors in the SSM were drawn from a Gaussian distribution in a range of $[-3\sigma, +3\sigma]$ to obtain a representative sample of the population. For further information on the bi-atrial SSM, the reader is referred to [7]. IAB was modeled by blocking conduction at the cells in BB located at the septal transition between RA and LA. An example of the atrial geometries is shown in Fig. 2. Each atrial geometry was placed in 25 pre-existing torso geometries derived from a human body statistical shape model [10]. In each of the atria-torso setups, the atria were rotated and translated by four different parameter combinations. The rotation angles were randomly drawn from a uniform distribution in a range of $[-10°, +10°]$ around the x-, y- and z-axis. The translation parameters were derived from a uniform distribution in a range of $[-10\,\text{mm}, +10\,\text{mm}]$ around the same three axes. Two of these setups per atria-torso combination were used for modeling healthy subjects, in the two remaining ones, IAB was simulated. In this way, we generated 9,800 12-lead ECG P waves (98 atrial geometries $\times$ 25 torso geometries $\times$ 4 rotation and translation settings) out of which 4,900 ECG signals reflect healthy individuals and 4,900 patients with IAB.

2.1.2 Electrophysiological Simulations

To generate large ECG datasets, simplified models such as the Eikonal model and the boundary element method (BEM) turned out to be a reasonable approach [8]. Thus, local activation times (LATs) for each node in the atrial geometry were calculated by solving the Eikonal equation with the FaMaS method [11]. Therefore, conduction velocities (CVs) and anisotropy ratios depending on seven different atrial regions as reported previously were assigned for each model [7] (see Tab. 1). The activation was initiated at the sino-atrial node at the junction of crista terminalis and the superior vena cava. A pre-computed Courtemanche et al. [3] action potential template was then shifted in time according to the LATs to derive the spatio-temporal distribution of the transmembrane voltage in the atria [8]. The ECG forward problem was solved by means of the BEM to calculate the body surface potentials [8]. The P waves were extracted at the standard electrodes positions for a 12-lead setup. For further information on the modeling approach, the reader is referred to [8].

Tab. 1: Parameters for the electrophysiological simulations

Atrial region	Conduction velocity	Anisotropy ratio
Interatrial connections	1093 mm/s	3.36
Right atrium	739 mm/s	2.11
Left atrium	946 mm/s	2.11
Valve rings	445 mm/s	2.11
Pectinate muscles	578 mm/s	3.78
Crista terminalis	607 mm/s	3.00
Inferior isthmus	722 mm/s	1.00

2.2 Evaluation of the Simulated P waves

The dataset was evaluated by analyzing the P wave duration, morphology and PTF-V1 automatically. P wave duration was calculated as the difference between the earliest P wave onset and latest offset across all 12 leads. P wave morphology was extracted by analyzing the peaks of the original and the inverted signal. According to the prominence and location of the detected peaks, positive and negative monophasic and bifid P waves as well as positive biphasic ($\pm$) and negative biphasic ($\mp$) P waves were distinguished. Contrary to the commonly applied definition of PTF-V1 as the product of the duration

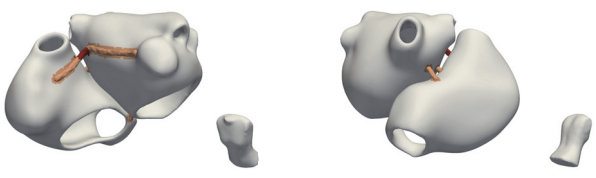

Fig. 1: Example of an atrial geometry derived from the bi-atrial SSM with four interatrial conduction pathways (displayed in orange). IAB at the septal transition between right and left atrium in BB is indicated in red.

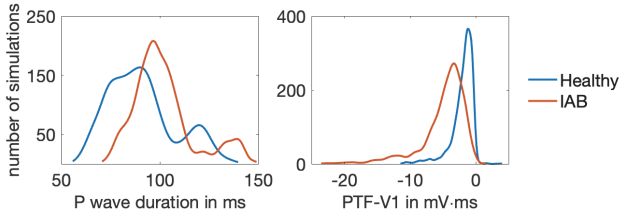

Fig. 2: Histograms of the results of P wave duration and PTF-V1 with distribution fit to a kernel distribution. Both feature values are increased for models with IAB compared to healthy models.

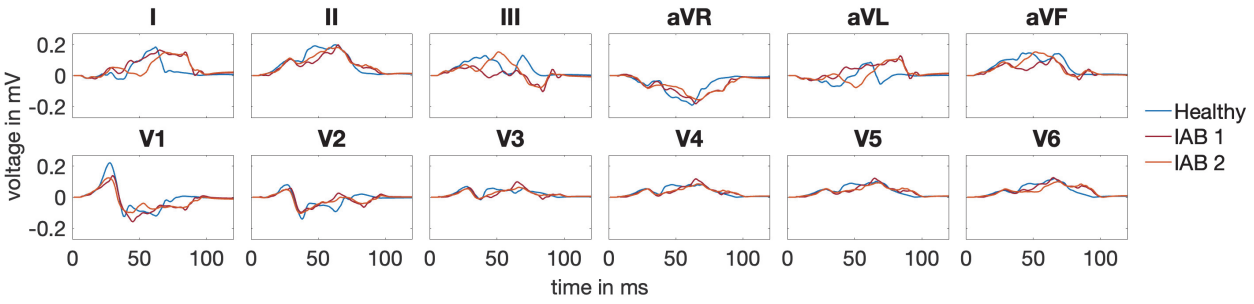

Fig. 3: Examples for the simulated P waves of the 12 lead ECG. The simulation result for a healthy model is shown in blue. Results for the same atrial model with IAB and two different rotation and translation parameters are shown in red and orange. Typical biphasic P wave morphology in case of IAB can be seen in lead III with variable shape. Lead III is bifid for the healthy model. Morphology in lead II and aVF is not biphasic in case of IAB in contrast to descriptions in literature. P wave duration is increased for models with IAB (92 ms and 94 ms) compared to the healthy model (85 ms).

and the amplitude of the negative deflection in lead V1, PTF-V1 was calculated by the integral of the negative deflection [5].

3 Results

Examples of the simulated P waves are shown in Fig. 3 for healthy models and models with IAB. Mean P wave duration was 90.66 ms for healthy models and 101.66 ms for models with IAB. Mean PTF-V1 was -2.0 mV·ms for healthy models and -4.9 mV·ms for models with IAB. A histogram of the P wave duration and PTF-V1 is shown in Fig. 2. The detected P wave morphology is shown in Fig. 4.

4 Discussion

We generated a large-scale in silico ECG dataset including IAB and compared the P wave features of models with IAB to healthy models. Our dataset can not only be used for feature analysis of IAB but fulfills also the requirements for ML applications and can be easily extended. The simulation results indicate a wide diversity in the morphology of ECG signals for patients with IAB. None of the investigated morphology features could be detected in all models. Due to a lack of a single and decisive feature, an analysis of all 12 leads is required for the diagnosis of IAB. The clinical diagnosis of IAB is based on a biphasic morphology in lead II, III and aVF and a bifid morphology in lead I and aVL [1, 2]. Only some of these features could be reproduced in silico. On the one hand, this shows that the retrograde activation of the LA leading to a biphasic morphology can be reproduced in silico. But also, this implies that the biphasic morphology observed for patients with IAB in lead II and aVF in the clinical setting is either not from the block in BB itself but the result of other pathological changes in the atria that are not represented in the SSM or results from a blockage in more than one interatrial bridge as proposed by Gao et al. [4].

Atypical IAB due to duration or morphology was first reported by Bayés de Luna et al. [1] and could be found in our dataset as well (see Fig. 5). Currently, the respecive signals are assigned to one of the six predefined categories by the automated algorithm either way. Further adaption of the algorithm and the used labels is needed to cover other morphology types as well. For models with IAB, P wave duration was increased compared to healthy models by 11 ms on average. However, only 636 out of 4,900 models exceeded the threshold for the clinical diagnosis of IAB (P wave duration $\geq$ 120 ms [1]). Nevertheless, the criterion was fulfilled with a higher prevalence for models with IAB compared to healthy models. Compared to the Copenhagen ECG study [9], the P wave durations in our study were already lower for healthy models. This suggests that the CVs might be overestimated and the results could be improved further by reducing the CVs or considering variability of CVs. PTF-V1 is considered a specific criterion for left atrial enlargement (LAE) [2]. We could show that PTF-V1 is also increased for models with IAB. Thus, further research is needed to distinguish between IAB and LAE since the underlying pathological changes and therefore the treatments are different. The results indicate further, that rotation and translation parameters of the atria may influence the morphology to the same extent as IAB. In our study, some healthy models satisfied the diagnostic criteria for IAB and for some of the models with IAB, none of the typical features reported for IAB could be detected (see Fig. 5).

Future in silico studies on IAB could include the consideration of further anatomical variability such as the location, number and shape of the interatrial conduction pathways. Additionally, partial IAB, different spatial blockage distributions and IAB

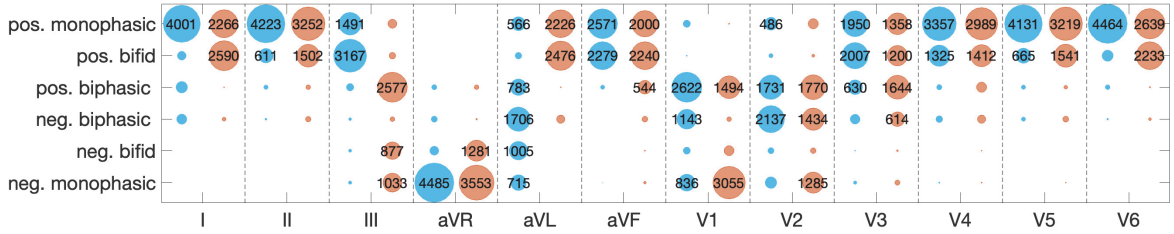

Fig. 4: Detected P wave morphology for healthy models (blue) and models with IAB (orange). An automated analysis to classify 6 different morphologies was performed. The respective number of simulations assigned to each morphology and lead is represented. In agreement with the clinical diagnosis criteria, biphasic morphology in lead III could be detected for most of the models with IAB.

in interatrial conduction pathways different than BB could be considered. By adding non-anatomical, functional changes such as different CV settings or CV slowing due to fibrotic infiltration in the remaining atrial tissue, the results could be extended further. The presented dataset could be used to investigate the relationship between the anatomy, rotation and translation of the atria and the morphology of the P wave. Furthermore, a comparison to other cardiac diseases (especially LAE) and the combination of LAE and IAB could help not only to improve the diagnosis of both pathologies but also to better understand the underlying pathological principles.

According to our study, the role of a biphasic P wave morphology for the diagnosis of IAB might have been overestimated in the past. Biphasic P wave morphology seems to be neither necessary nor sufficient for the diagnosis of IAB. An intense multi-dimensional feature analysis using machine learning techniques and including different measurements (morphology and duration) considering all 12 leads could help to increase the sensitivity of the diagnosis for IAB compared to the standard literature criteria by reducing the amount of missed IAB due to atypical morphology.

Author Statement

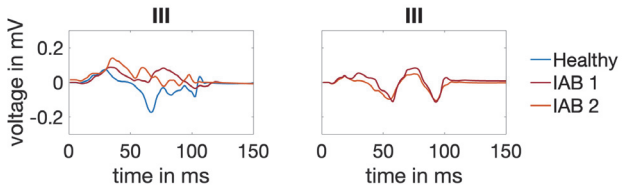

Fig. 5: Examples of atypical morphology in case of IAB in lead III. Left: Positive monophasic (orange) and positive bifid (red) signals for models with IAB, positive biphasic signal for a healthy model (blue). Right: no standard morphology label is suitable. According to [1], the signals should be classified as triphasic. In this study, the signals are classified by the algorithm as negative biphasic (red) and negative bifid (orange). Prominence of the second maximum at 75 ms in the orange signal is not sufficiently large to be detected by the algorithm.

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