Improving Clinical ECG-based Atrial Fibrosis Quantification With Neural Networks Through In Silico P waves From an Extensive Virtual Patient Cohort

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Abstract

Fibrotic atrial cardiomyopathy is characterized by a replacement of healthy atrial tissue with diffuse patches exhibiting slow electrical conduction properties and altered myocardial tissue structure, which provides a substrate for the maintenance of reentrant activity during atrial fibrillation (AF). Therefore, an early detection of atrial fibrosis could be a valuable risk marker for new-onset AF episodes to select asymptomatic subjects for screening, allowing for timely intervention and optimizing therapy planning. We examined the potential of estimating the fibrotic tissue volume fraction in the atria based on P waves of the 12-lead ECG recorded in sinus rhythm in a quantitative and non-invasive way. Our dataset comprised 68,282 P waves from healthy subjects and 42,227 P waves from AF patients with low voltage areas in the atria, as well as 642,400 simulated P waves of a virtual cohort derived from statistical shape models with different extents of the left atrial myocardium replaced by fibrosis. The root mean squared error for estimating the left atrial fibrotic volume fraction on a clinical test set with a neural network trained on features extracted from simulated and clinical P waves was 16.57 %. Our study shows that the 12-lead ECG contains valuable information on atrial tissue structure. As such it could potentially be employed as an inexpensive and widely available tool to support AF risk stratification in clinical practice.

1. Introduction

Disease mechanisms contributing to fibrotic remodeling of atrial tissue include an increased deposition of collagen strands and other extracellular matrix proteins in the interstitial space. The accumulation of collagenous septa implies the separation and electrical decoupling of myocytes and thus restricts the electrical depolarization wave to propagate via alternate conduction pathways. With increased conduction anisotropy, slowed conduction due to down-regulated gap junction proteins, and the formation of unidirectional conduction blocks, fibrotic patches provide an arrhythmogenic substrate for the initiation and maintenance of functional and anatomical re-entry patterns. Thus, an early and quantitative estimation of fibrotic atrial volume fractions could allow for stratifying the risk of new-onset atrial fibrillation (AF). Moreover, it could serve as a basis for suggesting susceptible patients for AF screening, choosing an appropriate treatment strategy, and reducing the risk of accompanying co-morbidities.

State-of-the-art techniques to quantify the extent of fibrotic tissue in the atria comprise late Gadolinium enhancement magnetic resonance tomography and electroanatomical voltage mapping. However, these methods are cost-intensive and invasive procedures. On the other hand, the 12-lead electrocardiogram (ECG) is a non-invasive, widely available, and easily acquirable tool to monitor and evaluate the cardiac function. We therefore investigate how well the extent of left atrial fibrotic volume can be estimated with machine learning algorithms based only on P waves of the 12-lead ECG.

To overcome the limitations of clinical ECG data in terms of annotation uncertainties, signal quality and the lack of a large and balanced dataset, we conducted multi-scale electrophysiological simulations in a previous study to create a well-controlled and extensive input dataset for a machine learning algorithm. In this regard, we had generated a synthetic dataset comprising 642,400 P waves by varying atrial and thoracic geometries, rotation angles, and conduction velocity settings as described in [1, 2]. Providing various P wave features extracted from the synthetic dataset to a neural network, we succeeded in estimating the left atrial fibrotic volume fraction with an average error of 10.7 % across the virtual population. In this multicenter translational study, we now examine how well the amount of left atrial fibrotic tissue can be estimated based on clinical ECGs from patients with a known history of paroxysmal and persistent AF.

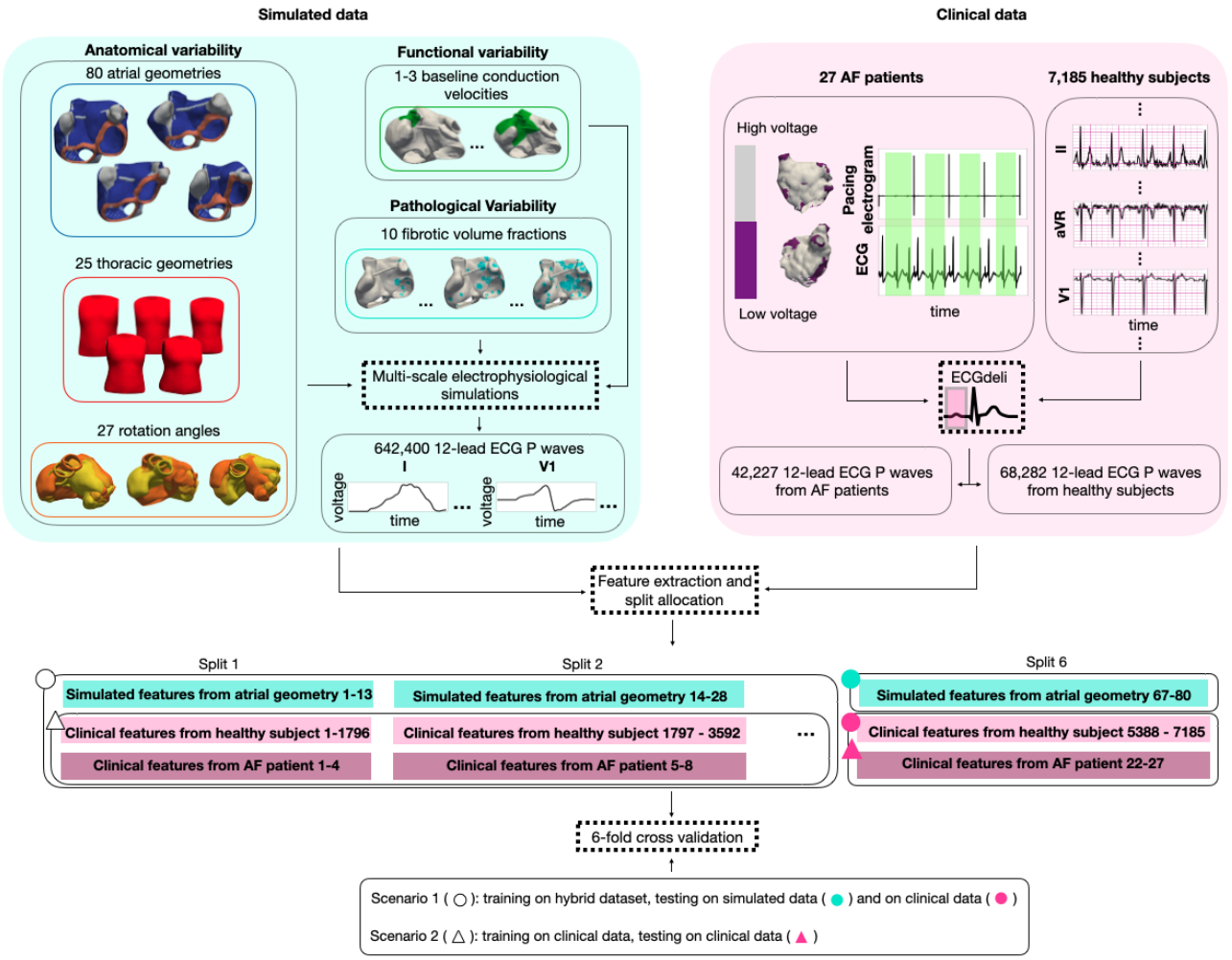

Figure 1. Clinical and simulated dataset used in this study. Simulated data were characterized by anatomical, functional, and pathological variability. Clinical signals originated from 27 AF patients and 7,186 healthy subjects. Features were extracted and the resulting dataset was divided into subsets to perform a 6-fold cross-validation with a neural network using two different training strategies: a hybrid dataset (dots) and only clinical P waves (triangle).

2. Methods

2.1. Simulated data

As described in previous work [1, 2] and displayed in Figure 1, we generated a synthetic dataset comprising 642,200 P waves of the 12-lead ECG in normal sinus rhythm in a cohort characterized by anatomical variability (i.e., 80 atrial anatomies, 25 thoracic anatomies, and 27 rotation angle combinations), functional variability (i.e., 1-3 baseline conduction velocity settings), and pathological variability (i.e., 10 different fibrotic volume fractions from 0 to 45 % of the left atrium). Realistic ECG noise as generated in [3] was added to the simulated signals before applying high- and lowpass filters with cut-off frequencies of 0.5 Hz and 150 Hz, respectively.

2.2. Clinical data

From 27 AF patients who underwent an electroanatomical mapping procedure at Städtisches Klinikum Karlsruhe and University Hospital Essen, bipolar electrograms as well as 12-lead ECGs in sensed paced rhythm were recorded. Patients provided informed consent and the study was approved by the institutional review boards. Detecting the activity at the pacing site from the electrograms allowed to select time windows of normal sinus rhythm activity in the ECG traces. ECGdeli [4] was applied to automatically delineate the P waves in the 12-lead ECGs in sinus rhythm. Furthermore, we calculated the fraction of fibrotic substrate in the left atrial endocardium for each patient by identifying the areas where bipolar peak-to-peak voltage was below 0.5 mV. P waves were also delineated

using ECGdeli in the 12-lead sinus rhythm ECGs of 7,185 healthy subjects from the public PTB-XL dataset [5].

In this way, a total of 68,282 single clinical P waves from 7,185 subjects in the control group and 42,227 single P waves from 27 patients with an extent of fibrotic left atrial areas between 7.05 % and 77.28 % were used as an input for the machine learning classifiers.

2.3. Machine learning classifier

The following P wave features were extracted from the simulated and clinical ECG datasets as described previously [1,2]: peak-to-peak amplitude in all 12 leads, P wave duration, P wave dispersion, P wave terminal force in lead V1, and the integral over the terminal 10, 20 and 30 ms of the ECG signal in all 12 leads. These features were provided to a feature-based feedforward neural network. The output quantity to be estimated by the network was the left atrial fibrotic area of the respective patient.

For the training of the regression network, we split the P wave feature data into 6 subsets. In each of them, clinical P wave features of 1796-1797 healthy subjects and 4-5 AF patients were combined with features extracted from the simulated dataset generated based on 13-14 different atrial geometries. We performed 6-fold cross-validation by employing one of these subsets at a time as a test set and using the remaining 5 sets for training and validation. Through this procedure, we ensured that P wave features extracted from one patient are only included in either of the training, validation or test set, and that the testing of the trained network is only performed based on the P waves from patients the network has never seen before.

For each split, a machine learning regression model was trained twice: once by only using features from the clinical ECGs during training and validation and once by also providing simulated data to evaluate whether the network benefits from in silico signals as an additional data source.

3. Results

The performance of the neural network is shown in Figure 2. In any case except for split 6, the estimation of the fibrotic extent was more accurate if simulated data were additionally included in the training set. The improvement when training the network with the hybrid dataset averaged over all clinical test set splits was around 1%.

The ground truth vs. the estimated fibrotic atrial volume fraction is depicted for all patient data in the different test sets combined in Figure 3. The root mean squared error between the estimated and ground truth fibrotic extent was 9.66 % and 16.57 % for the simulated and clinical test set on average, respectively. When only considering clinical data with a low voltage area fraction <45 % as was the case in the simulated dataset, the network performance error was comparable to the results in the simulated test sets and quantified to 12.28 %.

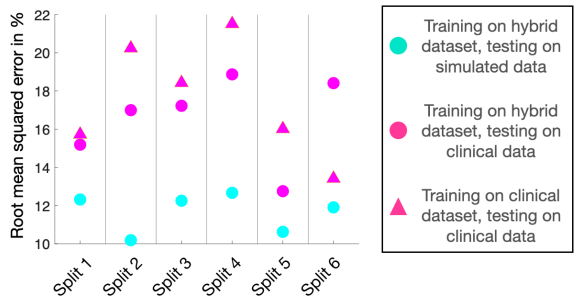

Figure 2. Performance of a neural network trained on a hybrid dataset (dots) and on clinical data only (triangle) when evaluated separately on a simulated (cyan) and clinical test set (magenta).

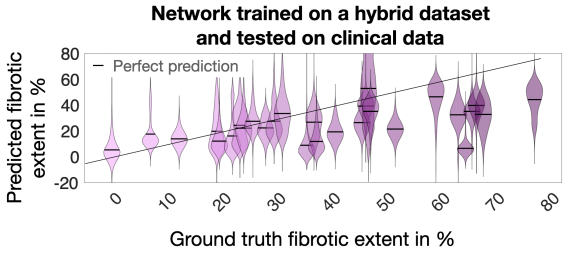

Figure 3. Ground truth vs. estimated fibrotic extent in the atria when training the neural network based on a hybrid dataset and testing it on clinical (magenta) signals.

4. Discussion and conclusion

In this work, we demonstrated the feasibility of non-invasively estimating the amount of fibrosis in the atria by using features from clinical 12-lead ECGs as an input to a feedforward neural network. The root mean squared error between the estimated and the ground truth fibrotic volume fraction on a test set composed of clinical signals was 17.56 % when using only clinically recorded ECGs during training of the network. The error was reduced to 16.57 % by additionally including simulated data. Compared to current state-of-the-art methods to quantify the fibrotic extent in the atria, our ECG-based estimation can be a reasonable indicator for fibrosis infiltrating the atrial myocardium, but does not provide quantitatively as accurate results as invasive mapping procedures or expensive imaging techniques.

To generate simulated signals at scale, yet at a reasonable computational cost, we drew on the Eikonal model as a propagation driver and on the infinite volume conductor as a simplified forward calculation method. On the one hand, the Eikonal model is capable of faithfully re-

producing local activation times obtained with the bidomain model.On the other hand, the infinite volume conductor was found to systematically overestimate P wave amplitudes in leads V1-V3 compared to the finite element method [6]. As this affects most of the features extracted from V1-V3 that were employed for the neural network, especially the amplitudes, a domain shift between the simulated and the clinical data for the affected features might have limited the benefits of providing more input variability through simulated signals during training.

The fibrosis distribution in the virtual patient cohort was set based on a spatial histogram of high image intensity ratios in late Gadolinium enhanced magnetic resonance images, as explained in more detail in [2]. Thus, the simulation dataset is mainly characterized by fibrotic patches on the posterior left atrial wall. Opposite to this, the clinical electroanatomical voltage maps employed for extracting the ground truth fraction of fibrosis on the endocardium mainly exhibit low voltage areas on the anterior left atrial wall [7]. Furthermore, the fibrotic volume fractions defined for the virtual patient cohort ranged only up to 45 %, whereas the maximum surface area fraction of low voltage electrograms was 77.28 %. Therefore, the lack of P wave features pertaining to high fibrotic extents in the in silico training set could have caused the underestimation of fibrotic volume fractions in patients characterized by large low voltage areas in the clinical test set and therefore reduced the overall network performance. This is also visible in Figure 3 as the estimated fibrotic extent complies with the ground truth values to a markedly higher degree for patients with low voltage areas $<$45 %.

Adding noise to the simulated data prior to feature extraction was important to reduce the estimation error with the hybrid training dataset as this contributes to closing the domain gap between clinical and simulated ECGs. When including features directly extracted from the raw simulated ECGs during training, the network's performance declined from 16.57 % (150 Hz lowpass cut-off frequency) to 17.40 % (without added noise and filtering) which is comparable to the performance in case the network is only trained on clinical data. Furthermore, choosing appropriate filter settings for all signals was necessary for a successful fibrosis estimation. Applying a lowpass filter with a cut-off frequency of 40 Hz instead of the chosen 150 Hz, the network performance could only be improved for 3 out of 6 splits when additionally providing simulated data for training. This highlights the need of preserving subtle ECG characteristics that might arise due to delayed and scattered depolarization of the tissue in fibrotic areas and the necessity of recording clinical signals of high quality.

Given the results of our study, the ECG constitutes a non-invasive and widely available tool in clinical practice to indicate the left atrial volume fraction of fibrotic tissue up to an uncertainty of around 16 %. Moreover, simulated signals of a virtual patient cohort covering anatomical, functional and pathological variability can contribute to reduce the estimation error.

Acknowledgments

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