Left Atrial Hypertrophy Increases P-Wave Terminal Force Through Amplitude but not Duration

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Abstract

P-wave morphology correlates with the risk for atrial fibrillation (AF). Left atrial (LA) enlargement could explain both the higher risk for AF and higher P-wave terminal force (PTF) in ECG lead V_1. However, PTF-V_1 has been shown to correlate poorly with LA size. We hypothesize that LA hypertrophy, i.e. a thickening of the myocardial wall, also contributes to increased PTF-V_1 and is part of the reason for the rather low specificity of increased PTF-V_1 regarding LA enlargement.

To show this, atrial excitation propagation was simulated in a cohort of four anatomically individualized models including rule-based myocyte orientation and spatial electrophysiological heterogeneity using the monodomain approach. The LA wall was thickened symmetrically in steps of 0.66 mm by up to 3.96 mm. Interatrial conduction was possible via discrete connections at the coronary sinus, Bachmann's bundle and posteriorly. Body surface ECGs were computed using realistic, heterogeneous torso models.

During the early P-wave stemming from sources in the RA, no changes were observed. Once the LA got activated, the voltage in V_1 tended to lower values for higher degrees of hypertrophy. Thus, the amplitude of the late positive P-wave decreased while the amplitude of the subsequent negative terminal phase increased. PTF-V_1 and LA wall thickening showed a correlation of 0.95. The P-wave duration was almost unaffected by LA wall thickening ($\Delta \leq 2$ ms).

Our results show that PTF-V_1 is a sensitive marker for LA wall thickening and elucidate why it is superior to P-wave area. The interplay of LA hypertrophy and dilation might cause the poor empirical correlation of LA size and PTF-V_1.

1. Introduction

The P-wave in the body surface ECG has long been used to gain insight into anatomy, function and dysfunction of the atria [1]. As a 12-lead ECG is routinely acquired non-invasively as part of a large number of examinations, ECG-derived measures represent ideal risk markers due to their availability and low associated costs [2]. These properties render ECG-based markers more attractive than alternatives like ultrasound, magnetic resonance imaging, electroanatomical mapping, or ECG imaging. Therefore, clinicians aim to stratify arrhythmia risk based on P-wave markers [3]. The assessment of morphological features of the P-wave is recommended in current guidelines for ECG interpretation [4] regarding the diagnosis of atrial abnormalities such as left or right atrial enlargement. The anatomy of the left atrium (LA) is of particular interest regarding the risk to develop atrial fibrillation (AF) as larger atria are more vulnerable to reentry in general. Therefore, left atrial enlargement (LAE) could explain both the higher risk to develop AF and higher P-wave terminal force (PTF) in ECG lead V_1 defined as the product of the duration and the amplitude of the terminal negative part of the P-wave. However, the criterion PTF-$V_1 > 4$ mVms correlates rather poorly with LA size in empirical studies. Truong et al. reported an accuracy of 51% using computed tomography as a reference [5].

The reasons for the rather poor performance of the PTF-V_1 and other P-wave markers (such as duration and amplitude) and a mechanistic link between anatomical properties and features of the P-wave are not understood, to date. A controlled *in vivo* study is hard to design because LA size cannot be adjusted in a single patient. Therefore, this study investigates the effect of LA hypertrophy on the P-wave in the body surface ECG *in silico*. The computa-

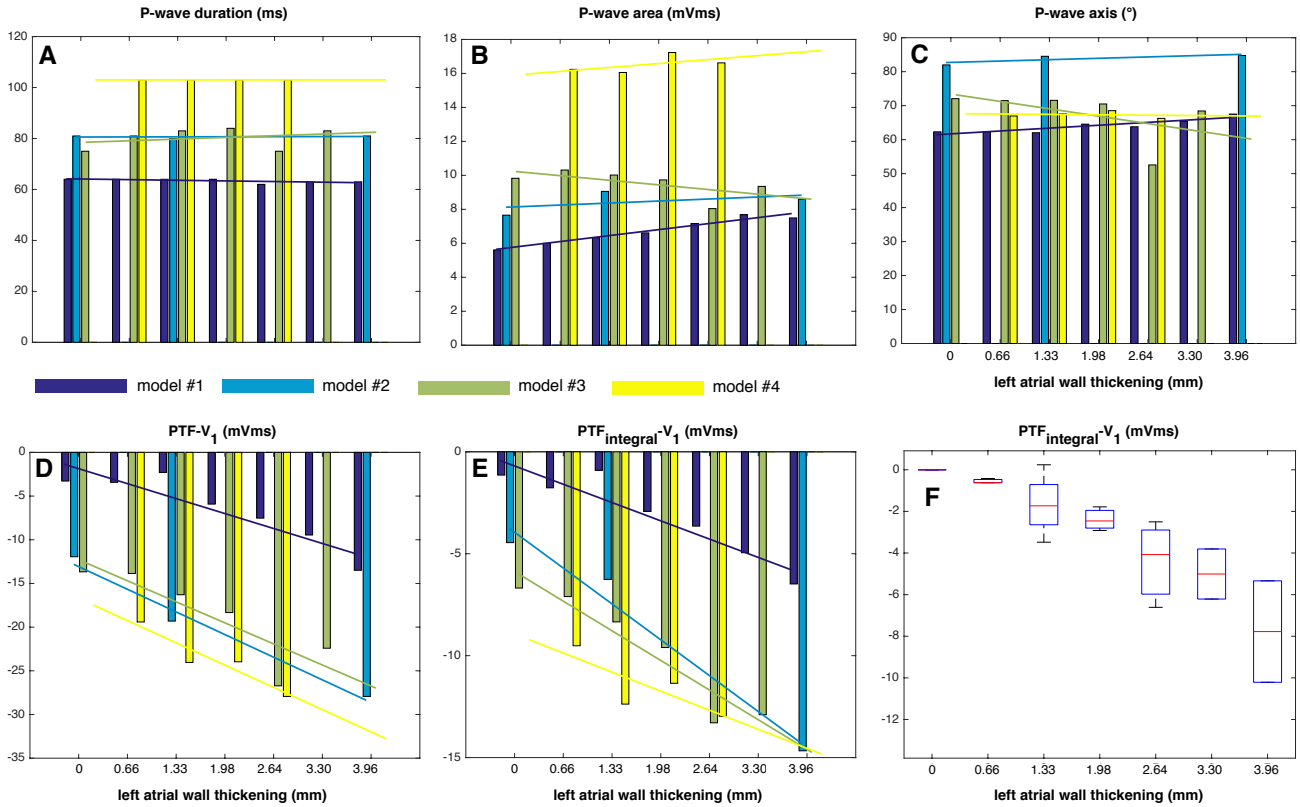

Figure 1. Effect of left atrial hypertrophy (wall thickening) on different P-wave markers. P-wave duration (A) and P-wave area (integral) (B) were measured in Einthoven lead II. P-wave axis (C) was determined based on leads aVF and I. P-wave terminal force in lead V_1 was measured by the product of amplitude and duration (D) as well as the integral (E) of the negative phase of the P-wave. Missing values were due to failure of torso mesh generation. Lines indicate a linear regression of the marker values for each model. (F) shows the difference in $PTF_{integral}$ in Wilson lead V_1 with respect to the non-hypertrophic baseline model. The missing baseline value for model #5 was linearly extrapolated.

tional approach being applied allows to dissect the effect of LA wall thickening, particularly on PTF-V_1, in a controlled environment: different degrees of hypertrophy can be simulated in the same subject's model.

2. Methods

The LA wall was thickened in four anatomical models to investigate the effect of LA hypertrophy. The subjects were between 19 and 50 years of age and had structurally healthy atria [6]. The voxel-based bi-atrial models covering the two atria, the trunks of the great vessels, and the blood within the atria had an isotropic resolution of 0.33 mm. The additional wall thickness due to hypertrophy was modeled equally and homogeneously on the endocardial and the epicardial side in steps of one voxel. Therefore, wall thickness was increased up to the initial value plus 3.96 mm in steps of 0.66 mm yielding seven different models variants. The dilation of one voxel layer was implemented such that voxels adjacent to LA voxels that were not RA voxels were marked as LA voxels. Reapplying this operation added one more voxel layer and so forth. Myocyte orientation in the atria and anatomical structures allowing for heterogenous electrophysiology [7] were annotated in the dilated models using previously described methods [8, 9]. The same holds for the discrete interatrial connections at the coronary sinus, Bachmann's bundle and posteriorly.

Excitation propagation was simulated using the monodomain solver *acCELLerate* [10, 11]. Numerical field calculation in the torso was conducted on tetrahedral meshes using a reduced bidomain approach in order to obtain body surface potentials [12].

3. Results

The LA wall was thickened to seven different degrees in four anatomically personalized models. The generation of tetrahedral torso meshes using *CGAL* [13] however failed in eight of the 28 cases. Therefore, some values are missing in Figure 1, which shows the effect of LA hypertrophy on different P-wave markers.

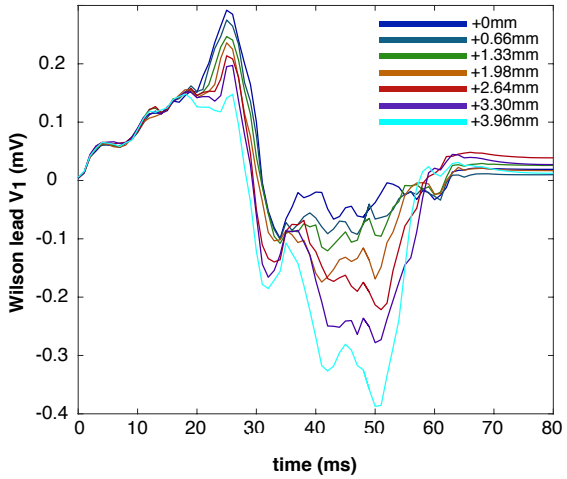

Figure 2. P-waves in Wilson lead V_1 for different degrees of LA wall thickening in model #1.

P-wave duration (PWD) (Figure 1A) was almost unaffected by LA wall thickening even though the latest activated regions were located in the LA for all non-hypertrophic models. For models #1, #2, and #4, the maximum difference in PWD for different wall thicknesses was 2 ms; for model #3, it was 9 ms. The P-wave area under the curve in lead II (Figure 1B) correlated with increased wall thickness due to an increase in amplitude. This relation was not consistent across models, however, with Pearson correlation coefficients ranging from 0.63 for model #3 to 0.98 for model #1. P-wave axis α was determined based on the amplitudes in leads aVF and I:

$$\alpha = \arctan\left(\frac{2}{\sqrt{3}}\frac{aVF}{I}\right) . \quad (1)$$

The axis did not show a consistent dependency on the degree of wall thickening with a positive correlation for models #1 and #2 and a negative correlation for models #3 and #4 (Figure 1C). The ECG in lead V_1 (Figure 2) reveals that during the early P-wave, no change was present because the LA was not yet activated. Once the LA got activated, the voltage in V_1 tended to lower values for higher degrees of hypertrophy. Thus, the amplitude of the (late) positive phase decreased while the amplitude of the subsequent negative phase increased. This translates to a strong and consistent correlation between LA wall thickness and PTF-V_1 with a mean correlation coefficient of –0.93 and a mean slope of –3.49 mVms per mm wall thickening (Figure 1D). Evaluating the integral of the negative phase of the P-wave in lead V_1 (PTF$_{integral}$-V_1) instead of the product of the duration and the amplitude (PTF-V_1) yielded comparable results with mean values of –0.95 for the correlation coefficient and a slope of –1.26 mVms per mm wall thickening (Figure 1E). The distribution of the increase in PTF$_{integral}$-V_1 (Figure 1E) with respect to the value obtained using the non-hypertrophic baseline models yielded a monotonic, rather robust relation, as well. The distribution for the classical definition of PTF-V_1 was similar but exhibited more interindividual variance (data not shown).

4. Discussion

The results obtained through computational modeling using a cohort of 4 anatomical models suggest that PWD is unaffected by LA hypertrophy and the effect on P-wave axis is highly dependent on the individual anatomy of the patient. PTF-V_1 seems to be a sensitive marker for LA wall thickening and was superior to evaluating the integral of the whole P-wave as only the amplitude of the negative P-wave was increased by a thickened LA wall and the amplitude of the positive phase was decreased towards its end. The evaluation of the integral of the negative phase of the P-wave in lead V_1 (PTF$_{integral}$-V_1) was more conclusive than considering the product of amplitude and duration (classical definition of PTF-V_1). The LA wall thickness has not been correlated with measured P-wave indices in clinical studies, so far. Thus, the findings of this study cannot be compared to sensitivity values observed in the general population *in vivo*.

A limitation of the presented study is the assumption of homogeneous hypertrophy across the LA which might not be the case *in vivo* as well as the assumption that the RA is not affected at all. Moreover, hypertrophy might be accompanied by fibrosis leading to a reduction of the source currents per volume. While additional interatrial connections might be present (particularly on the anterior side) their vicinity to Bachmann's bundle makes it unlikely that they alter the activation pattern dramatically [14]. The size of the virtual cohort of $n = 4$ models is small compared to most in vivo studies. However, a model population carries a significant advantage over using a single model result: the effect of characteristics specific to a single subject can be minimized by assessing a distribution of results. As a lot of modeling studies base their conclusions on a single anatomical model, the virtual cohort of four models is an important step forward. Considering that only anatomical variability of the subjects used to build the models was considered in this study gives confidence that the study cohort covers a good share of the populations variability.

LAE is commonly defined as an increased total volume of the LA rather than an increased myocardial volume. Intuitively, one would assume that the P-wave is prolonged by LA dilation while the signal amplitude (positive as well as negative) rather decreases. How pronounced these effects are actually remains to be seen. Particularly regarding PTF-V_1, the question is if the two counteracting effects balance each other or if e.g. the prolongation outweighs the decrease in amplitude leading to increased absolute PTF-V_1 values. Conceptually, LAE could also be

a combination of dilation and hypertrophy. For the ventricles, it is known that they respond to pressure overload in two phases. First, the increased pressure is compensated by hypertrophic remodeling. If the condition persists or worsens, the system decompensates and the ventricles dilate [15]. The same might be true for atrial pressure overload underpinned by the observation that the atrial wall is thinner in AF patients compared to the healthy population (2.1-2.5 mm vs. 2.3-2.9 mm) [16]. The two-stage mechanism could explain the contradicting findings regarding the sensitivity and specificity of PTF-V_1 with respect to the diagnosis of LAE [5, 17–21]. In that case, PTF-V_1 would be increased during the hypertrophic phase and potentially abate towards more moderate values once decompensation, and thus dilation, sets in. The effect of LA dilation will be assessed in a computational follow-up study.
In conclusion, it was shown that the P-wave markers PTF-V_1, and even more so PTF$_{integral}$-V_1, are sensitive to changes in left atrial wall thickness. The observations that the P-wave is drawn towards negative voltages in lead V_1 and that the PWD is unaffected provide mechanistic explanations why the aforementioned markers are superior. The interplay of LA hypertrophy and dilation might cause the poor empirical correlation of LA size and PTF-V_1.

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