ORIGINAL ARTICLE

Physiological variation in left atrial transverse orientation does not influence orthogonal P-wave morphology

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Background: It has previously been demonstrated that orthogonal P-wave morphology in healthy athletes does not depend on atrial size, but the possible impact of left atrial orientation on P-wave morphology remains unknown. In this study, we investigated if left atrial transverse orientation affects P-wave morphology in different populations.

Methods: Forty-seven patients with atrial fibrillation, 21 patients with arrhythmogenic right ventricular cardiomyopathy, 67 healthy athletes, and 56 healthy volunteers were included. All underwent cardiac magnetic resonance imaging or computed tomography and the orientation of the left atrium was determined. All had 12-lead electrocardiographic recordings, which were transformed into orthogonal leads and orthogonal P-wave morphology was obtained.

Results: The median left atrial transverse orientation was 87 (83, 91) degrees (lower and upper quartiles) in the total study population. There was no difference in left atrial transverse orientation between individuals with different orthogonal P-wave morphologies.

Conclusions: The physiological variation in left atrial orientation was small within as well as between the different populations. There was no difference in left atrial transverse orientation between subjects with type 1 and type 2 P-wave morphology, implying that in this setting the P-wave morphology was more dependent on atrial conduction than orientation.

KEYWORDS

atrial electrophysiology, atrial orientation, atrium, echocardiography, electrocardiography, P-wave morphology

Three different orthogonal P-wave morphologies have previously been characterized, suggested to represent different atrial depolarization paths (Holmqvist et al., 2008). Type 1: predominantly positive leads X and Y and predominantly negative lead Z, type 2: predominantly positive leads X and Y and biphasic lead Z (negative, positive), and type 3: predominantly positive lead X and biphasic leads Y (positive, negative) and Z (negative, positive) (Holmqvist, Platonov, Havmöller, & Carlson,

2007). Although it is plausible that other factors, such as morphological characteristics of the atria, affect P-wave morphology, our group has previously demonstrated that the distribution of P-wave morphologies in healthy athletes does not depend on the size of the atria (Petersson et al., 2014). However, the possible impact of the *orientation* of the left atrium (LA) on P-wave morphology is, to our knowledge, not known. The current study was designed to explore if LA transverse orientation

differs between subjects with different P-wave morphology, with the hypothesis being that if the transverse orientation of the LA varies significantly, it may influence orthogonal P-wave morphology. In order to increase the heterogeneity in LA orientation, four different populations were analyzed—patients with atrial fibrillation (AF), patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), healthy athletes and healthy volunteers.

1 | METHODS

The study was retrospective by design. The exclusion criteria were an active atrium-stimulating pacemaker, the use of class I or class III antiarrhythmic drugs during the last five half-lives prior to the electrocardiographic (ECG) recording, nonsinus rhythm or inadequate ECG and a cardioversion within 1 week before the ECG recording. After exclusion, 191 subjects remained (Table 1): 47 consecutive patients with AF scheduled for catheter ablation, 21 consecutive patients diagnosed with definite ($n = 12$) or borderline ($n = 9$) ARVC, 67 healthy athletes and 56 healthy volunteers.

1.1 | AF patients

Records of all patients who had undergone catheter ablation of AF at Skåne University Hospital in Lund between May 2000 and November 2011 were screened for inclusion in this study. Prior to the ablation procedure, cardiac magnetic resonance imaging (MRI) or computed tomography (CT) scans had been done to map the anatomy of the pulmonary veins. In total, 399 ablations had been performed between May 2000 and November 2011. Of these, 293 first-time ablations were identified.

1.2 | ARVC patients

Consecutive patients diagnosed with ARVC at Skåne University Hospital in Lund between the years 2003 and 2014 were screened for inclusion. Patients with definite or borderline ARVC according to the 2010 Task Force diagnostic criteria were included (Marcus et al., 2010). The patients had either sought care because of symptoms like syncope, ventricular tachycardia or premature ventricular contractions or were discovered through family screening, initiated because of sudden cardiac death or ARVC diagnosis in a family member. In total, 21 patients were included.

1.3 | Healthy athletes and volunteers

These subjects were retrieved from a previous study by Steding et al., (2010). There were 131 subjects in the study: 30 soccer players (twelve females), 23 handball players (twelve females), 18 elite triathletes (six females), and 60 healthy volunteers (20 females). None had cardiovascular disease. All were nonsmokers and had no cardioactive medication.

The study complies with the Declaration of Helsinki and the research protocol was approved the Regional Ethical Committee.

1.4 | Data analysis

1.4.1 | Cardiac MRI

All subjects examined with cardiac MRI were scanned in supine position using a 1.5-T scanner (Philips Intera CV, Philips, Best, The Netherlands) with a cardiac synergy coil. The orientation of the LA in the thorax was obtained using either of two types of sequences; Survey sequences (typical settings: repetition time 2.1 ms, echo time 0.8 ms, flip angle 50°, spatial resolution of 1.76 mm × 1.76 mm and slice thickness 10 mm with no slice gap) or Balanced turbo field echo sequences (B-TFE) (typical settings: repetition time 3.16 ms, echo time 1.6 ms, flip angle 80°, spatial resolution of 1.35 mm × 1.35 mm and slice thickness 5 mm with no slice gap).

1.4.2 | Cardiac CT

AF patients examined with CT were scanned in supine position using a Philips CT scanner with a spatial resolution of typically 0.5 mm × 0.5 mm and slice thickness of 1 mm.

1.4.3 | LA transverse orientation

A transverse image slice was selected in a plane between the left and right inferior pulmonary veins where the LA appeared the most prominent. One vector was then drawn along the long-axis of the LA and another vector was drawn between the ventral part of the vertebral column and the sternum in the same plane (Fig. 1). The angle between the two vectors was then computed. This was a novel approach to determine the LA transverse orientation, which had not been used or validated in other studies.

FIGURE 1 A transverse magnetic resonance image slice showing how the left atrial transverse orientation was computed. The horizontal line represents the long-axis of the left atrium and the vertical line represents the vector between the vertebral column and the sternum. The arrows indicate the pulmonary veins visible in this slice

1.4.4 | ECG acquisition and analysis

Standard, 12-lead ECGs for all subjects were digitally retrieved from the two major ECG databases in Skåne (Infinity MegaCare and GE Healthcare MUSE). We collected the ECG most recent to the MRI/CT date that showed stable sinus rhythm. Data analysis was performed using custom-made software running on MATLAB R2013b for Mac OS X (The MathWorks, Inc., Natick, MA, USA). Using the inverse Dower transform, the acquired ECGs were transformed into derived vectorcardiograms for orthogonal lead analysis (Carlson et al., 2005). Subsequently, a 0.5-Hz high-pass filter and a 50-Hz band-stop filter were applied. QRS complexes were automatically detected and clustered together using a cross-correlation coefficient of $p > .9$. The P waves were extracted using a 250-ms time-window preceding the QRS complexes. The time window was manually altered in cases with a long PQ time. All P waves were time-shifted to achieve maximum correlation. P waves with a cross-correlation coefficient of $p > .9$ were grouped together. The P waves in each cluster were then signal-averaged. The beginning and end of the actual P wave were manually defined. The method is described in more detail elsewhere (Holmqvist et al., 2007). Finally, the morphology of the signal-averaged P waves was classified as one of the three types described in the introduction. P waves that did not fall into any category were denoted “atypical.”

1.5 | Statistics

Data are presented as mean $\pm$ standard deviation (SD) when normally distributed, otherwise as median (lower, upper quartiles). LA transverse orientation was assumed to be restricted to a range between 0 and 180 degrees and was thus treated as a nonparametric variable. Student's *t* test was used for normally distributed data, Mann-Whitney's test was used for nonparametric data and Fisher's exact test was used for nominal data. For correlation analysis between LA transverse orientation and other variables, Spearman's rank correlation coefficient, ρ , was computed. All statistical analyses were performed using IBM SPSS Statistics version 22.0.0.1 for Mac OS X.

The MR and CT images were analysed using a freely available software application (Segment 1.9 R2688 for Windows; <http://segment.heiberg.se>) (Heiberg et al., 2010).

2 | RESULTS

Twelve subjects (five AF patients, one ARVC patient, three healthy volunteers, and three healthy athletes) had a P-wave morphology other than 1 or 2 and were left out of further analyses.

2.1 | LA transverse orientation

There was no significant difference in LA transverse orientation between subjects with type 1 and type 2 P-wave morphology in any study group (Table 2). In the largest group, the athletes, we found no significant correlations between any factor and LA transverse orientation (Table 3).

TABLE 1 All subjects

	All (<i>n</i> = 191)
Age (years)	34 (25, 52)
Male	118 (62%)
P-wave morphology (1/2)	102 (53%)/77 (40%)
BMI (kg/m ²)	24.6 $\pm$ 3.3
LA transverse orientation (°)	87 (83, 91)
PQ time (ms)	163 $\pm$ 25
P-wave duration (ms)	130 $\pm$ 17

Median (lower and upper quartiles) and mean $\pm$ standard deviation. Only P-wave morphology types 1 and 2 are included. BMI, body mass index; LA, left atrial.

However, in AF patients, age was correlated with LA transverse orientation ($\rho = -.325$, $p = .03$). The same was true for the healthy volunteers ($\rho = -.289$, $p = .03$). No other factors were significantly correlated with LA transverse orientation (data not shown). There was no difference in median LA transverse orientation between men and women in any group (e.g. 89 vs. 89 degrees, $p = .48$, for the athletes).

We performed a test for interobserver variability in LA transverse orientation determination on 16 randomly selected cases and found a maximum difference of $\pm 5^\circ$ between two observers (data not shown).

2.2 | Age, body mass index and P-wave duration

In the largest group (the healthy athletes) the median age was higher among individuals with type 2 P-wave morphology (31 years vs. 24 years, $p = .03$). In the patient groups, the median body mass index (BMI) was higher in subjects with type 2 P-wave morphology than among them with type 1 P-wave morphology (e.g. 28.4 [25.1, 30.7] vs. 24.8 [22.4, 25.3] kg/m² in the AF patients, $p = .01$). In the healthy volunteers, the median P-wave duration was longer in subjects with type 2 morphology (132 [124, 139] ms vs. 125 [118, 132] ms, $p = .02$). Please refer to Table 2.

3 | DISCUSSION

The main finding of the present study was that the physiological interindividual variation in LA transverse orientation does not affect orthogonal P-wave morphology.

Several factors influence P-wave morphology. It has been shown that the localization of the origin of the right atrial depolarization affects P-wave morphology—i.e. a more superiorly located leading pacemaker produces a positive P wave in lead aVF. It is also plausible that different exit paths from the sinus node play a part (Boineau et al., 1988; Monfredi, Dobrzynski, Mondal, Boyett, & Morris, 2010). The morphology of the terminal part of the P wave is determined by the localization of the LA breakthrough site (Holmqvist et al., 2008). One could suspect that atrial volumes would affect P-wave morphology type, but our group has previously shown that this is not the case in young, healthy athletes (Pettersson et al., 2014).

TABLE 2 (A) AF patients. (B) ARVC patients. (C) Healthy athletes. (D) Healthy volunteers

	All (n = 47)	P-wave morphology 1 (n = 11; 23%)	P-wave morphology 2 (n = 31; 66%)	p
(A)				
Age (years)	60 (50, 65)	50 (41, 64)	60 (51, 65)	.22
Male	28 (60%)	8 (73%)	19 (61%)	.72
BMI (kg/m ²)	26.9 ± 4.4	24.8 (22.4, 25.3)	28.4 (25.1, 30.7)	.01
LA transverse orientation (°)	84 (78, 89)	89 (78, 94)	83 (78, 88)	.12
PQ time (ms)	165 ± 24	166 (148, 186)	157 (144, 183)	.52
P-wave duration (ms)	147 ± 16	157 (145, 161)	149 (133, 156)	.27
	All (n = 21)	P-wave morphology 1 (n = 12; 57%)	P-wave morphology 2 (n = 8; 38%)	p
(B)				
Age (years)	42 (27, 65)	30 (26, 50)	54.0 (35, 66)	.12
Male	15 (71%)	8 (67%)	7 (88%)	.60
BMI (kg/m ²)	23.6 (22.4, 26.5)	23.1 (21.7, 23.7)	26.4 (23.7, 26.6)	.02
LA transverse orientation (°)	86 (84, 90)	87 (84, 91)	85 (80, 89)	.31
PQ time (ms)	164 ± 30	157 (144, 185)	163 (141, 190)	.62
P-wave duration (ms)	129 ± 15	124 (120, 129)	131 (119, 146)	.24
	All (n = 67)	P-wave morphology 1 (n = 49; 73%)	P-wave morphology 2 (n = 15; 22%)	p
(C)				
Age (years)	24 (21, 31)	24 (21, 30)	31 (24, 35)	.03
Male	38 (57%)	26 (53%)	11 (73%)	.24
BMI (kg/m ²)	23.4 (21.9, 25.0)	23.4 (21.5, 24.5)	23.7 (22.4, 25.6)	.15
LA transverse orientation (°)	89 (87, 91)	89 (86, 91)	89 (88, 92)	.20
PQ time (ms)	163 ± 25	164 (145, 179)	162 (153, 185)	.54
P-wave duration (ms)	123 ± 13	124 (113, 132)	128 (121, 134)	.08
	All (n = 56)	P-wave morphology 1 (n = 30; 54%)	P-wave morphology 2 (n = 23; 41%)	p
(D)				
Age (years)	33 (26, 45)	30 (25, 36)	36 (26, 52)	.07
Male	35 (63%)	17 (49%)	18 (51%)	.15
BMI (kg/m ²)	24.2 ± 3.0	23.7 ± 2.7	25.0 ± 3.4	.12
LA transverse orientation (°)	85 (82, 91)	87 (84, 92)	84 (80, 91)	.07
PQ time (ms)	159 ± 22	163 (144, 170)	158 (144, 170)	.69
P-wave duration (ms)	126 ± 13	125 (118, 132)	132 (124, 139)	.02

Median (lower and upper quartiles) and mean ± standard deviation. Analyzed with Student *t* test and Mann–Whitney and Fisher's exact test. Only P-wave morphology types 1 and 2 are included. BMI, body mass index; LA, left atrial.

TABLE 3 Correlations between LA transverse orientation and age, BMI, PQ time, and P-wave duration in the largest group (athletes)

	<i>ρ</i>	<i>p</i>
Age	−.034	.79
BMI	−.148	.23
PQ time	−.104	.40
P-wave duration	−.031	.80

Spearman's rank correlation coefficient, *ρ*. BMI, body mass index.

The groups analyzed in the present study were chosen because of their different atrial characteristics. Patients with AF are known to have structural remodeling of the atria (Platonov, Mitrofanova,

Orshanskaya, & Ho, 2011). Several studies in animal models of ARVC report the presence of fibrofatty replacements in the atrial myocardium (Basso et al., 2004; Fox, Maron, Basso, Liu, & Thiene, 2000). Human data are sparse, but case reports point in the same direction (Nogami et al., 1990; Takemura et al., 2008). Athletes tend to have physiologically larger atria (Pelliccia et al., 2005).

3.1 | LA transverse orientation

The focus of the current study was to specifically investigate the possible impact of LA transverse orientation on P-wave morphology type. Despite the different constitutions of the groups, the variability in LA transverse orientation was relatively small in all groups—the lower and

upper quartiles for the total study population were 83 and 91 degrees, respectively, with the range being 66 to 100 degrees. The current study shows that this relatively small physiological interindividual variance in LA transverse orientation was not sufficient to affect P-wave morphology classification. Thus, the observed difference in P-wave morphology is primarily influenced by other factors than atrial orientation.

3.2 | Further analysis of LA transverse orientation

We found indications for a possible negative correlation between age and LA transverse orientation. The reason for this finding remains to be explained. To our knowledge, no one has previously systematically studied the physiological variation in LA orientation. In a somewhat similar study, Engblom et al. investigated the relationship between the electrical and anatomical axes of the left ventricle and found no significant correlation in the transverse plane. They did however find a significant correlation between age and the anatomical axis of the left ventricle in the transverse plane (Engblom et al., 2005). In both the current study and the study by Engblom et al., the direction of the anatomical axis of the LA and left ventricle, respectively, in the transverse plane was rotated counterclockwise with increasing age.

3.3 | P-wave morphology versus age, BMI and P-wave duration

In keeping with previously published results from our group, P-wave morphology type 2 was more common among older healthy subjects (Havmoller et al., 2007). The reason why we only observed this pattern in the healthy volunteers may be attributed to a combination of power and age range. One can speculate that the higher prevalence of type 2 P-wave morphology in older subjects may be an expression of age-related structural changes in the heart, such as fibrosis.

AF and ARVC patients with type 2 P-wave morphology had a higher BMI than patients with type 1 P-wave morphology. In previous studies, increasing BMI has indeed been reported to correlate with increasing P-wave terminal force (Magnani et al., 2012), which is roughly equivalent to P-wave morphology type 2. The observed higher BMI in patients with P-wave morphology type 2 may be speculated to depend on fibrofatty replacement of the atria, which would affect atrial conductivity. A higher BMI, like the presence of P-wave morphology 2, could also be speculated to covary with an increased disease burden.

The observation that healthy volunteers with type 2 morphology had a longer P-wave duration has been noted earlier (Pettersson et al., 2014), and could possibly be explained by a different interatrial conduction pathway. The trend was similar in the athlete group. We did not find this difference in P-wave duration in the other groups, and this could likely be explained by lower power.

3.4 | Limitations

The same technique for assessing LA transverse orientation was used in both MR and CT images. Ideally there would have been a subgroup with both MR and CT images for comparing the obtained anatomical

axis between the modalities. However, all examinations were clinically motivated and no subject had performed both examinations.

4 | CONCLUSIONS

The variation in LA transverse orientation is small within different populations as well as between these populations. There is no difference in LA transverse orientation between subjects with type 1 and type 2 P-wave morphology.

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