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Sex-related electrocardiographic differences in patients with different types of atrial fibrillation: Results from the SWISS-AF study

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ABSTRACT

Background: Sex-related electrocardiographic differences are a well-known phenomenon, but not their expression in patients with atrial fibrillation (AF). In this study we aim to assess the presence of significant sex-related differences in ECG features, with particular attention to P-wave parameters, of a large cohort of patients affected by different types of AF.

Methods: A 5-min resting 16-lead ECG was evaluated for 1119 AF patients in sinus rhythm. The durations of the main ECG waves and intervals were measured for both atrial and ventricular activity. Moreover, the beat-to-beat P-wave variability was computed for lead II and for the first principal component (PC1) computed across the 16 leads. The percentage of variance explained by PC1 was computed.

Results: Males compared to females showed significantly longer RR interval (1.02 ± 0.16 s vs 0.97 ± 0.15 s, $p < .001$), PQ interval (191 ± 34 ms vs 183 ± 35 ms, $p = .008$), QRS duration (105 ± 17 ms vs 98 ± 13 ms, $p = .021$), significantly lower percentage of variance explained by PC1 and P-wave variability. Males with paroxysmal AF compared to females with paroxysmal AF had significantly longer RR interval (1.01 ± 0.17 s vs 0.96 ± 0.14 s, $p < .001$), shorter QTc (388 ± 27 ms vs 402 ± 27 ms, $p < .001$), lower P-wave variability in PC1. Males with persistent AF compared to females with persistent AF had significantly shorter QTc interval (396 ± 30 ms vs 407 ± 26 ms, $p = .019$), longer PQ interval (194 ± 35 ms vs 182 ± 30 ms, $p = .037$), higher V1 terminal force (2.1 ± 1.2 mV*ms vs 1.8 ± 1 mV*ms, $p = .007$), lower percentage of variance explained by PC1.

Conclusions: AF patients present with several sex-related ECG differences. Consequently, sex should be taken into account when developing ECG algorithms identifying patients at risk for AF progression.

1. Introduction

Atrial fibrillation (AF) is the most frequent clinical arrhythmia and is associated with significant costs, morbidity and reduced quality of life [1].

Previous studies have reported several sex-related differences in the prevalence, clinical presentation, associated comorbidities, and therapy outcomes of patients with AF [2]. Firstly, the age-related prevalence of AF is lower in women than in men. Secondly, women with AF have a worse quality of life and are more symptomatic than men [2]. Moreover, different studies have reported that female sex is an independent risk factor for stroke, cardiovascular disease and death in patients with AF [2,3]. Sex-related differences in relation with the susceptibility of AF have been also reported. In contrast, very little is known about electrocardiographic (ECG) differences between men and women presenting with different types of AF [4].

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The aim of this study was to assess the presence of significant sex-related differences in ECG features, with particular attention to P-wave parameters, of a large cohort of patients affected by different types of AF enrolled in the Swiss-AF study, a prospectively-designed cohort study [5].

2. Methods

2.1. Swiss-AF dataset

Swiss-AF is an observational cohort across 13 centers in Switzerland, including 2415 patients with paroxysmal, persistent or permanent AF. The study protocol, aims and patients' demographics have been reported elsewhere [5]. In brief, at enrollment all patients underwent a clinical examination, blood sampling, cerebral magnetic resonance imaging (cMRI), cognitive assessments, quality of life assessment and disability evaluation, AF-related medical resource use and costs. In addition, a 5-min resting 16-lead ECG (the standard 12 leads plus 2 precordial right side leads and 2 precordial back leads) was recorded (sample rate: 1 kHz, signal bandwidth 0.04-387 Hz with a resolution of 1 μV/bit) using CS-200 Excellence and CS-200 Touch devices (Schiller AG, Baar, Switzerland). Each procedure was repeated annually during follow-up, except for blood sampling and cMRI that were repeated every 2 years. The study protocol was approved by the local ethical committees and informed written consent was obtained from each participant.

2.2. ECG core laboratory

All recorded ECGs were stored at each participating center and then uploaded to a central server. In this study, only the ECGs performed at the time of enrollment were considered. A selection of 10 s of each ECG signal was reviewed by two electrophysiologists (G.C. and A.A) and classified according to the main rhythm present in the signal. Rhythm was classified as following: sinus rhythm (SR), atrial fibrillation (AF) or other rhythms (that included atrial tachycardia, atrial flutter, or rhythm induced by atrial pacing). During rating, the clinicians were blinded to each other. In case of disagreement, adjudication was done by consensus. Only the recordings during SR were analyzed in the present study. Out of 1215 SR recordings, 96 were excluded for the following reasons: poor signal quality ($N = 63$), frequent supraventricular extrasystoles ($N = 6$), incomplete clinical data ($N = 27$). Patients with pacemaker were included in the analysis only if they presented spontaneous P-waves. The patients were categorized into paroxysmal or persistent AF following clinical diagnosis at enrollment (Fig. 1). Paroxysmal AF was defined as AF that terminates spontaneously or with intervention within 7 days of onset. Persistent AF was defined as AF that is sustained continuously beyond 7 days [6]. A cardiac implantable electronic device (CIED) was present in 109 patients (10%). The values of the ventricular parameters (RR, PQ, QRS, QTc) of these subjects were excluded from analysis. Patients with CIED were included in the atrial analysis exclusively if they presented with spontaneous P-waves.

2.3. ECG preprocessing

ECG was filtered with a high-pass filter (Butterworth, 4th-order, fc = 0.5 Hz) to reduce baseline wander, with a low-pass filter (FIR, Hamming window, fc = 80 Hz) to reduce high-frequency/muscle interferences and with a Power Line Removal filter (50 Hz). Once beat detection was obtained by an algorithm similar to the Pan Tomkins' applied on lead V5, where ventricular activity is more evident, ventricular and atrial analysis were performed on averaged waveforms [7].

2.4. Ventricular analysis

In order to obtain an average beat, an alignment procedure was applied [8]. A beat window was defined around the R peak from 50 ms to 500 ms before and after the peak, respectively. A cross-correlation function was computed between each beat and all the others to evaluate which beats were more representative of the recording. The 20 beats with the highest cross-correlation mean value were averaged to obtain a template. Each beat was then correlated with the template and aligned according to the lag at which the cross-correlation function was maximal. Only beats with a maximum cross-correlation coefficient larger than 0.8 were included in the further analysis. An average beat was computed for each lead. In order to merge the information from all the lead, a ventricular template (V_t) was defined as in Eq. (1):

$$V_t = \sum_{l=1}^{L} M_l^2 \tag{1}$$

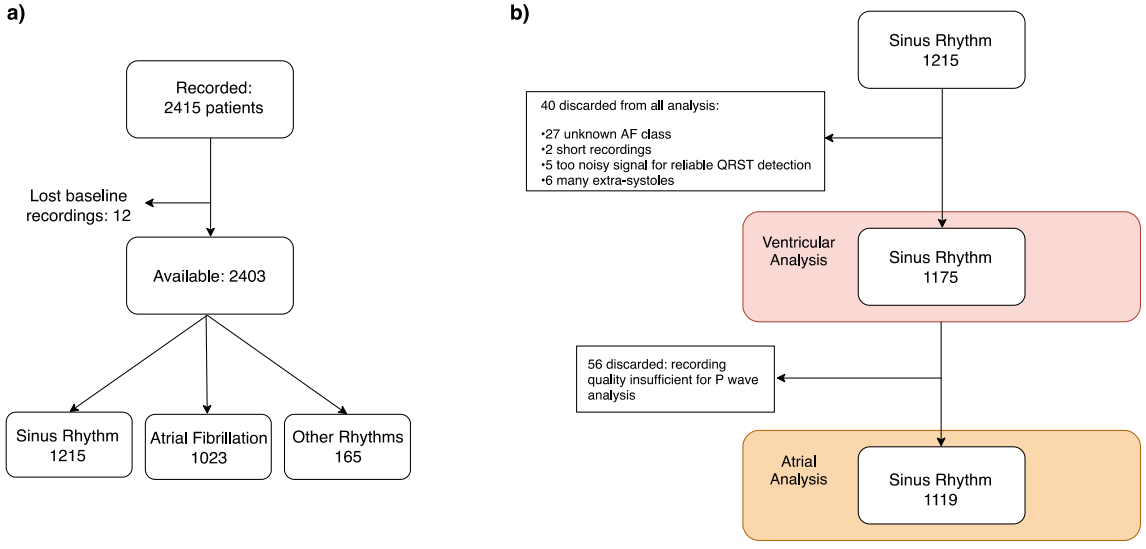

Fig. 1. Rhythm classification and workflow: a) Distribution of the patients in the three classes of sinus rhythm, atrial fibrillation and other rhythms, based on the prevailing rhythm at baseline. b) At the beginning of analysis, 40 recordings were discarded for lack of data, poor signal quality, or supraventricular extra-systoles; other 56 were not considered in the atrial analysis because the noise level did not allow P-wave analysis.

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where L is the number of leads, in this study L = 16, and M_l is the average beat for the l-th lead computed as:

$$M_l = \frac{1}{N}\sum_{n=1}^{N} B_{n,l} \quad (2)$$

where $B_{n,l}$ is the n-th beat in the l-th lead and N is the overall number of averaged beats (see Fig. S1 for details). The obtained V_t was processed to automatically detect the fiducial points. The averaging procedure was performed to reduce the noise effect and to make detection of fiducial points more reliable. QRS duration and QT interval were obtained as the difference between the correspondent points. QTc was calculated following the Bazett's formula [9], as in Eq. (3).

$$QTc = \frac{QT}{\sqrt{RR}} \quad (3)$$

2.5. Atrial analysis

Knowing the average TQ and QRS durations from the ventricular analysis, we could accurately select the segment containing the P-wave, positioned after the end of the T wave and before the start of the following QRS complex. The procedure to obtain an average P-wave was similar to that described in section *Ventricular analysis* but lead II was used. Lead II was chosen as P-waves are usually easily identifiable and positive. After alignment, we obtained the 16 averaged P-waves on which an automatic algorithm was applied to detect the beginning and end of the P-waves. The P-wave duration was computed as the difference between the median offset and the median onset in the 16 leads (see Fig. S2 for details). The PQ interval was computed on the template as the difference between the beginning of the P-wave and the beginning of the following QRS complex. The P-wave terminal force in lead V1 (*V1 tf*) was measured as the integral of the terminal negative part of the P-wave [10]. From the end of the wave, the first negative point (if present in the second half of the wave) was found and considered the ending point of the integral. Going backward, the first not positive point was selected as the starting point of the integral.

2.6. Waves detection

An algorithm was implemented to detect the ECG fiducial points. The first derivative was computed to find the points with maximum positive/negative slope. Based on the order of appearance, the concavity of the wave was assessed. Two straight lines were drawn from the detected points, with slopes that were a fraction of the first derivative value. The fraction, empirically chosen, changed according to the assessed wave, going from 1/50 for the Q wave to 1/4 for the P and T waves. The beginning and end points were identified as the points with the maximal distance from the line (see Fig. S3 for details).

2.7. P-wave variability

P-wave variability was computed using 2 methods:

- the Euclidean distance between each beat and the following one, normalized for the root mean square of the second one;
- the similarity index, computed as the cosine of the angle between each beat and the following one [11].

To reduce the influence of noise, we excluded all the beats whose maximum cross-correlation coefficient with the average P-wave was smaller than 0.9. The Euclidean distance and the similarity index were computed for each beat and the mean and Median Absolute Deviation (MAD) value of all the values were computed. This procedure was applied both on lead II and on the first principal component (PC) [12]. The procedure was iterated beat to beat.

2.8. Principal component analysis

The principal component analysis (PCA) is a statistical method to transform a set of possibly correlated variables into a set of uncorrelated ones (called principal components) by means of an orthogonal transformation [13]. The PCA is an iterative procedure that derives step by step the component explaining the largest variance inside the dataset, with the constraint of being orthogonal to the preceding ones. This method is often used to reduce the dimensionality of a dataset minimizing information loss by means of selecting only few components that explain almost all the variation present in the dataset [13]. In our study, we applied the PCA in order to consider and synthesize the information of all the leads. For the P variability, we computed the first component of every beat and measured its variation over time [11,12]. Furthermore, we noted the percentage of variance expressed by the first component (called variance explained by PC1) and considered it a measure of the correlation between the morphological waves in the 16 leads. The mean and MAD values on the whole recording were computed.

2.9. Statistical analysis

A general linear model was run to determine the effect of gender on the computed parameters after controlling for the following covariates: age, height, weight, class of AF, history of coronary artery disease, of pulmonary vein ablation, of sleep apnea, of diabetes and of thyroid disease. The procedure was performed for the whole population and in subgroups with the same type of AF. Furthermore, a general linear model was run to determine the effect of AF type on the computed parameters after adjusting for sex, age, height, weight, history of heart failure, transient ischemic attack (TIA), anticoagulant drugs (OAC/DOAC, that stand for, respectively, oral anticoagulants and direct-acting oral anticoagulants), amiodarone and antiarrhythmic drugs Ic (AADs). After adjustment for the previously stated covariates, the adjusted p-values are reported in the results, whereas data are unadjusted mean and standard deviation. For the categorical variables, the two-proportion z-test was used to compare the populations.

A p-value <.05 was considered statistically significant. All analyses were performed using Matlab R2017a (The MathWorks, Natick, MA). Statistical analysis was performed using SPSS v.25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study population features

Out of 2415 participants, 2403 had an ECG recording available at the first visit. Among them, 1215 showed SR as main rhythm and were thus analyzed for the purpose of this study (Fig. 1).

Baseline characteristics of the study population are shown in Table 1. Male predominance was observed (766 males, 69%). Males were significantly younger as compared to females (70 ± 9 vs. 73 ± 8 years, $p < .001$). Moreover, males were more frequently affected by persistent AF compared to females (34% vs. 28%, $p = .031$). No significant differences were found in the rate of males and females treated with Ic antiarrhythmic drugs. Patients with paroxysmal AF received more frequently Ic AADs, while patients with persistent AF were treated more often with amiodarone. Regarding the history of interventions to restore sinus rhythm, we found that 31.6% of paroxysmal patients and 37.3% of persistent ones had at least one ablation of the pulmonary veins;

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Table 1
Study population characteristics: values are given as average (std) or number (%). The asterisks mark the statistically significant differences.

Study population							
Characteristics	All $N = 1119$	Males $N = 766$	Females $N = 353$	p-value males vs. females	Paroxysmal $N = 762$	Persistent $N = 357$	p-value paroxysmal vs. persistent
Males	766 (68.5%)	766 (100%)	0 (0%)	–	506 (66.4%)	260 (72.8%)	0.028*
Age	70.8 (8.5)	69.7 (8.6)	73.1 (7.9)	<0.001*	71.2 (8.5)	70.0 (8.5)	0.030*
Height [cm]	172.5 (9.0)	176.4 (6.8)	163.9 (6.8)	<0.001*	172.1 (8.9)	173.3 (9.2)	0.027*
Weight [Kg]	81.5 (15.8)	85.2 (14.4)	73.6 (15.8)	<0.001*	80.7 (15.8)	83.1 (15.6)	0.019*
BMI [Kg/m^2]	27.4 (4.7)	27.3 (4.3)	27.4 (5.6)	0.862	27.2 (4.8)	27.6 (4.5)	0.228
Class of AF:							
- Paroxysmal	762 (68.1%)	506 (66.1%)	256 (72.5%)	0.031*	762 (100%)	0 (0%)	–
- Persistent	357 (31.9%)	260 (33.9%)	97 (27.5%)	0.031*	0 (0%)	357 (100%)	–
AF duration [months]	54.3 (68.7)	54.3 (64.9)	54.1 (76.4)	0.966	55.6 (69.5)	51.4 (66.9)	0.347
History of:							
- Coronary Artery Disease	274 (24.5%)	224 (29.2%)	50 (14.2%)	<0.001*	185 (24.3%)	89 (24.9%)	0.813
- Valvular Disease	89 (8.0%)	61 (8.0%)	28 (7.9%)	0.986	57 (7.5%)	32 (9.0%)	0.393
- Heart Failure	188 (16.8%)	129 (16.8%)	59 (16.7%)	0.974	102 (13.4%)	86 (24.1%)	<0.001*
- PV ablation	374 (33.4%)	277 (36.2%)	97 (27.5%)	0.003*	241 (31.6%)	133 (37.3%)	0.067
- Sleep Apnea	131 (11.7%)	114 (14.9%)	17 (4.8%)	<0.001*	86 (11.3%)	45 (12.6%)	0.528
- Hypertension	725 (64.8%)	482 (62.9%)	243 (68.8%)	0.051	480 (63.0%)	245 (68.6%)	0.062
- Diabetes	144 (12.9%)	109 (14.2%)	35 (9.9%)	0.034*	101 (13.3%)	43 (12.0%)	0.574
- Peripheral Artery Disease	65 (5.8%)	50 (6.5%)	15 (4.2%)	0.103	46 (6.0%)	19 (5.3%)	0.634
- Renal Failure	170 (15.2%)	110 (14.4%)	60 (17.0%)	0.258	114 (15.0%)	56 (15.7%)	0.759
- Thyroid Disease	147 (13.1%)	69 (9.0%)	78 (22.1%)	<0.001*	93 (12.2%)	54 (15.1%)	0.192
- Stroke	115 (10.3%)	79 (10.3%)	36 (10.2%)	0.948	85 (11.2%)	30 (8.4%)	0.144
- TIA	82 (7.3%)	51 (6.7%)	31 (8.8%)	0.223	66 (8.7%)	16 (4.5%)	0.005*
- Previous CIED	109 (9.7%)	65 (8.5%)	44 (12.5%)	0.037*	78 (10.2%)	31 (8.7%)	0.414
Drug therapy:							
- OAC/DOAC	963 (86.1%)	657 (85.8%)	306 (86.7%)	0.682	638 (83.7%)	325 (91.0%)	<0.001*
- Amiodarone	254 (22.7%)	177 (23.1%)	77 (21.8%)	0.631	136 (17.8%)	118 (33.1%)	<0.001*
- Digitalis	15 (1.3%)	10 (1.3%)	5 (1.4%)	0.881	7 (0.9%)	8 (2.2%)	0.124
- Ic AAD	79 (7.1%)	54 (7.0%)	25 (7.1%)	0.984	65 (8.5%)	14 (3.9%)	0.001*
- Beta Blockers	721 (64.4%)	484 (63.2%)	237 (67.1%)	0.195	491 (64.4%)	230 (64.4%)	0.997
-Calcium Antagonist	213 (19.0%)	144 (18.8%)	69 (19.5%)	0.767	139 (18.2%)	74 (20.7%)	0.324

18.1% of paroxysmal subjects and 76.2% of persistent ones had at least one electrical cardioversion; 16.1% of paroxysmal patients and 22.7% of persistent subjects had at least one radiofrequency ablation of the isthmus region. The time from the first AF diagnosis to the patients' enrollment was comparable between males and females and between patients with paroxysmal and persistent AF.

Table 2
Comparison Male/Female and Paroxysmal/Persistent: values are given as average (std). The asterisks mark the statistically significant differences.

Study population							
Characteristics	All N = 1119	Males N = 766	Females N = 353	p-value males vs. females	Paroxysmal N = 762	Persistent N = 357	p-value paroxysmal vs. persistent
RR [ms]	1000 (160)	1015 (164)	968 (146)	<0.001*	995 (159)	1012 (161)	0.119
QRS [ms]	103 (16)	105 (17)	98 (13)	0.021*	102 (16)	104 (18)	0.072
QTc [ms]	395 (29)	391 (28)	404 (27)	0.050	393 (28)	399 (30)	0.122
PQ [ms]	189 (35)	191 (34)	183 (35)	0.008*	188 (35)	191 (34)	0.219
P dur [ms]	122 (21)	123 (21)	120 (22)	0.083	121 (20)	124 (24)	0.056
*V1 tf [mV*ms]*	2.1 (1.1)	2.2 (1.2)	2.0 (1.0)	0.415	2.2 (1.1)	2.0 (1.1)	0.088
Mean of the beat-to-beat EuclDist Lead II	33.5×10^{-2} (11.6×10^{-2})	33.4×10^{-2} (11.6×10^{-2})	$0.33.6\times10^{-2}$ (11.7×10^{-2})	0.795	33.2×10^{-2} (11.8×10^{-2})	34.1×10^{-2} (11.3×10^{-2})	0.206
MAD of the beat-to-beat EuclDist Lead II	5.4×10^{-2} (1.9×10^{-2})	5.4×10^{-2} (1.9×10^{-2})	5.4×10^{-2} (1.9×10^{-2})	0.740	5.3×10^{-2} (1.9×10^{-2})	5.5×10^{-2} (1.8×10^{-2})	0.181
Mean of the beat-to-beat similarity Lead II	94.3×10^{-2} (3.6×10^{-2})	94.3×10^{-2} (3.6×10^{-2})	94.3×10^{-2} (3.6×10^{-2})	0.999	94.4×10^{-2} (3.6×10^{-2})	94.1×10^{-2} (3.6×10^{-2})	0.186
MAD of the beat-to-beat similarity Lead II	1.6×10^{-2} (1.0×10^{-2})	1.6×10^{-2} (0.9×10^{-2})	1.6×10^{-2} (1.0×10^{-2})	0.736	1.6×10^{-2} (1.0×10^{-2})	1.7×10^{-2} (0.9×10^{-2})	0.181
Mean of the e×plained variance by PC1	74.2 (10.2)	73.8 (10.3)	75.2 (9.9)	0.011*	73.9 (10.2)	75 (10.1)	0.078
MAD of the e×plained variance by PC1	2.06 (0.90)	2.05 (0.88)	2.08 (0.94)	0.623	2.05 (0.91)	2.07 (0.88)	0.936
Mean of the beat-to-beat EuclDist PC1	23.4×10^{-2} (9.8×10^{-2})	22.8×10^{-2} (9.6×10^{-2})	24.7×10^{-2} (10.1×10^{-2})	0.046*	23.3×10^{-2} (9.8×10^{-2})	23.7×10^{-2} (9.8×10^{-2})	0.480
MAD of the beat-to-beat EuclDist PC1	4.7×10^{-2} (2.1×10^{-2})	4.6×10^{-2} (2.1×10^{-2})	4.9×10^{-2} (2.2×10^{-2})	0.093	4.7×10^{-2} (2.2×10^{-2})	4.8×10^{-2} (2.1×10^{-2})	0.693
Mean of the beat-to-beat similarity PC1	97.0×10^{-2} (2.3×10^{-2})	97.1×10^{-2} (2.3×10^{-2})	96.8×10^{-2} (2.4×10^{-2})	0.395	97.0×10^{-2} (2.3×10^{-2})	96.9×10^{-2} (2.3×10^{-2})	0.478
MAD of the beat-to-beat similarity PC1	1.0×10^{-2} (0.8×10^{-2})	1.0×10^{-2} (0.8×10^{-2})	1.1×10^{-2} (0.8×10^{-2})	0.429	1.0×10^{-2} (0.8×10^{-2})	1.0×10^{-2} (0.8×10^{-2})	0.495

V1 tf stands for V1 terminal force; *EuclDist* stands for Euclidean Distance; *MAD* stands for median absolute value; *PC1* stands for first principal component.

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3.2. Sex-related ECG features assessment

ECG features according to patients' sex are shown in the Table 2. Males presented with significantly longer RR (1.02 ± 0.16 s vs 0.97 ± 0.15 s, $p < .001$), PQ interval (191 ± 34 ms vs 183 ± 35 ms, $p = .008$), QRS duration (105 ± 17 ms vs 98 ± 13 ms, $p = .021$), after adjusting for clinical covariates (see Fig. S4). Among the whole population, 12% of males and 5% of women had a spontaneous QRS interval longer then 120 ms. Females presented with significantly higher mean of the beat-to-beat Euclidean distance in the first PC ([24.7 ± 10.1] x 10^{-2} vs [22.8 ± 9.6] x 10^{-2}, $p = .046$) and percentage of variance explained by the first PC (75.2 ± 9.9 vs 73.8 ± 10.3, $p = .011$), as depicted in Fig. S5. As shown in Fig. S6, the frequency distribution of P wave duration was similar in males and females. In 13.5% of male and 15% female patients the P wave duration was equal or shorter than 100 ms.

3.3. Sub-analysis according to the clinical type of AF

ECG parameters of patients with paroxysmal and persistent AF are shown in Table 2. After adjusting for covariates, no significant difference was found between paroxysmal and persistent AF both in the whole population and in the subgroups of males and females.

When considering the clinical type of AF for males and females separately, similar results to the whole population were obtained, even if less significative comparisons were found (see Table 3). In particular, in the subgroup of paroxysmal AF, males compared to females had significantly longer RR interval (1.01 ± 0.17 s vs 0.96 ± 0.14 s, $p < .001$), shorter QTc (388 ± 27 ms vs 402 ± 27 ms, $p < .001$), and lower P-wave variability in PC1. Among the persistent patients, males compared to females had significantly shorter QTc interval (396 ± 30 ms vs 407 ± 26 ms, $p = .019$), longer PQ interval (194 ± 35 ms vs 182 ± 30 ms, $p = .037$), higher V1 terminal force (2.1 ± 1.2 mV*ms vs 1.8 ± 1 mV*ms, $p = .007$), and lower percentage of variance explained by PC1. While the PQ duration and the V1 terminal force were found significantly different only in the persistent group, the trend was also present in the paroxysmal subset.

4. Discussion

To our knowledge, this is the first study assessing sex-related ECG features in patients with different types of AF. The main findings of our analysis are: 1) patients with AF present with significant sex-related ECG differences; 2) these differences affect numerous parameters of both atrial and ventricular activity, such as the RR interval, QRS duration, PQ interval, mean of the beat-to-beat Euclidean distance in the first PC and percentage of variance explained by the first PC; 3) ECG parameters show differences between males and females inside each AF type subgroup.

4.1. ECG sexual differences in patients with AF

Sex-related differences in ECG signals are a well-known phenomenon [14]. Indeed, in the general population the corrected QT interval (QTc) is significantly longer in females than males. Furthermore, it has been shown that the development of this sex-related behavior is related with the age and hormonal factors. In fact, while male and female have similar QT values during childhood, after puberty and throughout early adulthood QT interval becomes shorter in males until returning to female values around the age of 50 years [14]. Regarding atrial parameters, there is, instead, no clear correlation between estrogens and P wave characteristics. Dogan et al. found that P-wave parameters did not change in postmenopausal women when compared to premenopausal women [15]. Karabag et al. found significant differences for P-wave dispersion and the minimal P-wave duration according to the phase of menstrual cycle. However, even if they found an inverse relation between estrogen levels and P-wave dispersion, the correlation between them was not statistically significant [16]. Parikh et al. studied the effects of reproductive period duration and number of pregnancies on midlife ECG indices, reporting small but significant changes in P-wave characteristics. However, they also stated that many factors could contribute to this behavior, thus the role of sex hormones is not clear [17].

Table 3
Comparison Male/Female in paroxysmal and persistent subgroups: values are given as average (std). The asterisks mark the statistically significant differences.

Study population						
Characteristics	Males Paroxysmal $N = 506$	Females Paroxysmal $N = 256$	p-value paroxysmal males vs. paroxysmal females	Males Persistent $N = 260$	Females Persistent $N = 97$	p-value persistent males vs. persistent females
RR [ms]	1010 (165)	963 (141)	<0.001*	1024 (161)	980 (158)	0.257
QRS [ms]	104 (16)	98 (14)	0.058	106 (19)	98 (12)	0.178
QTc [ms]	388 (27)	402 (27)	<0.001*	396 (30)	407 (26)	0.019*
PQ [ms]	190 (34)	184 (37)	0.055	194 (35)	182 (30)	0.037*
P dur [ms]	122 (19)	120 (22)	0.225	125 (23)	122 (24)	0.284
*V1 tf [mV*ms]*	2.2 (1.2)	2.0 (1.1)	0.068	2.1 (1.2)	1.8 (1.0)	0.007*
Mean of the beat-to-beat EuclDist Lead II	32.8 ×10^{-2} (11.8 ×10^{-2})	33.8 ×10^{-2} (11.8 ×10^{-2})	0.300	34.5 ×10^{-2} (11.2 ×10^{-2})	33.1 ×10^{-2} (11.5 ×10^{-2})	0.298
MAD of the beat-to-beat EuclDist Lead II	5.2 ×10^{-2} (1.9 ×10^{-2})	5.5 ×10^{-2} (2.0 ×10^{-2})	0.150	5.6 ×10^{-2} (1.8 ×10^{-2})	5.2 ×10^{-2} (1.8 ×10^{-2})	0.110
Mean of the beat-to-beat similarity Lead II	94.4 ×10^{-2} (3.6 ×10^{-2})	94.3 ×10^{-2} (3.6 ×10^{-2})	0.571	94.0 ×10^{-2} (3.6 ×10^{-2})	94.3 ×10^{-2} (3.6 ×10^{-2})	0.463
MAD of the beat-to-beat similarity Lead II	1.5 ×10^{-2} (1.0 ×10^{-2})	1.6 ×10^{-2} (1.0 ×10^{-2})	0.244	1.7 ×10^{-2} (0.9 ×10^{-2})	1.6 ×10^{-2} (0.9 ×10^{-2})	0.275
Mean of the e×plained variance by PC1	73.6 (10.3)	74.3 (10.2)	0.302	74.2 (10.4)	77.4 (8.9)	0.044*
MAD of the e×plained variance by PC1	2.0 (0.9)	2.1 (1.0)	0.189	2.1 (0.9)	2.0 (0.9)	0.231
Mean of the beat-to-beat EuclDist PC1	22.5 ×10^{-2} (9.6 ×10^{-2})	24.8 ×10^{-2} (10.0 ×10^{-2})	0.048*	23.4 ×10^{-2} (9.6 ×10^{-2})	24.6 ×10^{-2} (10.4 ×10^{-2})	0.275
MAD of the beat-to-beat EuclDist PC1	4.6 ×10^{-2} (2.2 ×10^{-2})	4.9 ×10^{-2} (2.2 ×10^{-2})	0.059	4.7 ×10^{-2} (2.1 ×10^{-2})	4.8 ×10^{-2} (2.2 ×10^{-2})	0.837
Mean of the beat-to-beat similarity PC1	97.2×10^{-2} (2.2 ×10^{-2})	96.7 ×10^{-2} (2.4 ×10^{-2})	0.212	96.9 ×10^{-2} (2.4 ×10^{-2})	96.9 ×10^{-2} (2.2 ×10^{-2})	0.900
MAD of the beat-to-beat similarity PC1	0.9 ×10^{-2} (0.8 ×10^{-2})	1.1 ×10^{-2} (0.8 ×10^{-2})	0.396	1.0 ×10^{-2} (0.8 ×10^{-2})	1.0 ×10^{-2} (0.8 ×10^{-2})	0.703

V1 tf stands for V1 terminal force; *EuclDist* stands for Euclidean Distance; *MAD* stands for median absolute value; *PC1* stands for first principal component.

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In this study, different ECG parameters were evaluated in relation to the patient's sex to better characterize sex-related differences in AF patients. Similar to previous studies, our analysis confirms the existence of sexual differences regarding RR interval and QRS duration between males and females affected by AF.

The sex-related difference in the RR duration has already been reported in the literature, but the explanation is still not univocally shared. Salama and Bett report that the higher heart rate likely reflects an intrinsic difference, as women have higher vagal tone and lower heart rate variability than men [18]. Burke et al. compared males and females before and after an autonomic blockade and proved that the difference appears to be associated with a gender difference in exercise capacity rather than intrinsic gender related properties of the sinus node or differences in autonomic tone [19]. Beckers et al. state that the difference in RR between males and females is probably due to a mix of factor, such as: difference in the sympathetic and vagal modulation, hormones and physical characteristics, stroke volume [20]. While a shorter QRS for women is reported in literature [21], there is no consensus on the physiological reasons behind. Simonson et al. considered it a possible effect of smaller heart dimensions in women [22]. However, Hnatkova et al. reported that QRS duration seems to be independent of lean body mass and also likely independent of heart sizes. They speculated that QRS shortening in women could be caused at the myocytes level by differences in the distribution of ion channels [23].

There was no significant difference in QTc interval after adjustment for covariates, probably due to the high average age of the population (71 ± 9 years) that suggests a less important role of sexual hormones. In a previous study focusing on sex-related ECG differences in healthy young athletes, longer P-wave duration and PQ interval were observed in males [24]. It was also reported that sex differences of ECG features were not completely explained by variations in body size. Consistent with a recent report by Nielsen et al. 14% of our patients showed a P wave duration of 100 ms or less, being more frequent in women than men [25]. In the Copenhagen ECG study, patients with very short P wave (<90 ms) were mostly female, had a particularly high risk of developing atrial fibrillation, stroke, and risk of cardiovascular death as high as those patients with prolonged P wave >120 ms. The mechanism postulated by Nielsen et al. was that a more rapid conduction time may provide a substrate for reentry in the early stages of the arrhythmia, related to electrical and structural remodeling. However, our population was on average 15 years older than the ECG Copenhagen cohort, had an history of paroxysmal or persistent atrial fibrillation and many were on antiarrhythmic drugs. Therefore, it is possible that these patients have different electrophysiological properties possibly related to still unknown genetic variants. Differently from previous studies, we also assessed sex differences in the beat-to-beat P-wave morphological variability (beat-to-beat Euclidean distance, similarity and percentage of variance explained by first principal component among leads), a set of indexes connected to the probability of AF onset and worsening [26]. These indexes are based on the assumption that AF patients sustain electrophysiological and/or structural remodeling of the atria, leading to a more chaotic propagation of the signal [27]. It has been reported that these indexes may be valuable in identifying patients prone to paroxysmal AF [25–27]. Recent computer modeling work by Pezzuto et al. indicated that beat-to-beat variability is related to presence and quantity of heterogeneous conduction, in combination with the intrinsic variability in the earliest activation site location in the sino-atrial node [28]. In our study, the mean of the beat-to-beat Euclidean distance in the first PC was significantly higher in the female population, suggesting a higher degree of fibrosis. Possible indirect clinical confirmation of that has been found by Li et al. who observed higher degree of fibrotic atrial remodeling in women compared to men [29]. This result is interesting considering that no significant differences emerged in the duration of the AF between males and females.

4.2. ECG features of patients with different types of AF

The identification of the clinical stage of AF (pathology progression) and the discrimination between paroxysmal and persistent AF is of utmost importance while assessing the therapeutic strategy and subsequent outcomes. Nearly all previous studies have focused on the identification of AF susceptibility or have correlated P-wave morphology to prognosis, but only few studies have analyzed sex-related ECG differences among patients with different clinical types of AF in SR [30]. Differently from these studies, Swiss-AF cohort included patients with known paroxysmal and persistent AF. We computed some indexes reported in the literature as related to the risk of AF, such as QRS duration, P-wave duration, PQ interval and beat-to-beat P-wave variability [26,31]. This was based on the consideration that the progression from the paroxysmal to the persistent type of AF could elicit ECG abnormalities and differences similar to those present between healthy subjects and patients with AF. El-Chami et al. found an association between QRS prolongation and AF susceptibility in patients with left ventricular dysfunction; they suggested that a longer QRS could reflect a generalized higher myocardial fibrosis, providing the substrate for AF [31]. Moreover, a prolonged QT interval has often been associated with an increased risk of AF [32]. The underlying pathophysiological mechanism is not clear: Mandyam et al. suggested that this observation could be related to aberrations in the refractoriness of both atrium and ventricle or to enhanced activity of the late sodium channel [32].

Regarding P-wave characteristics, we hypothesized that the beat-to-beat P-wave variability is able not only to predict and detect AF episodes, but also to differentiate between different types of AF, supposing that the progression of AF corresponds to a higher remodeling and consequent P-wave morphological variability. P-wave duration, PQ interval, P-wave terminal force in V1 and beat-to-beat P-wave variability have often been associated with the risk of AF and are considered a surrogate of higher atrial conduction time, due to either atrial enlargement or slower conduction [10,26].

Neither ventricular-related parameters, nor P-wave characteristics were able to discriminate patients with different types of AF in the studied population. A possible explanation is related to the different drug therapies used when the patient is known to suffer from paroxysmal or persistent AF.

The parameters showing a significantly different behavior between males and females in the whole population had a similar trend when comparing males to females in the paroxysmal and persistent groups (see Table 3). For the PQ interval, we found a significant difference between males and females in the whole population and in the persistent subgroup. Even if this difference was not statistically significant in the paroxysmal group, the trend is however present. The PQ interval is usually longer in men [33]. Furthermore, its prolongation is also linked with higher risk of AF in men. In women, instead, a higher risk of AF is linked with both short and long PQ [34]. Since the studied population consists of AF patients, we expect a longer PQ in men in comparison to both women and men without AF. For the female population we expect a shorter PQ than men and a PQ duration falling in the tails of the physiological range of female population: indeed 4% of men and 8% of women had a PQ shorter than the 5th percentile of the whole PQ distribution. We found a significant males/females difference in the persistent group, when AF is more stable and so men are more likely to have a prolonged PQ, while in women the presence of both short and long PQs lowers the average for the female population.

5. Limitations

Our study has certain limitations. It was conducted in a population of patients with heterogeneous clinical characteristics, which included fewer women than men, diminishing the statistical power of the analysis.

This study included only AF patients in SR. This could lead to an underrepresentation of patients in advanced disease and explain why

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there was no significant difference between paroxysmal and persistent AF. Moreover, the time needed to return in SR was not available in all patients. Therefore, it was not possible to differentiate between early-persistent and long-standing persistent AF.

We did not have information about the presence of bundle branch block in the ECGs, limiting the significance of the QRS duration analysis.

Sex-related P-wave parameters were not assessed in a control group of healthy patients without AF. Some parameters were not available at the time of the study, such as left atrium dimension. Finally, no information on the progression of AF from baseline to visit 1 were available.

6. Conclusions

Patients with AF present with significant SR sex-related ECG parameters differences. Consequently, sex should be taken into account when developing ECG algorithms identifying patients at risk for AF progression.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.12.053.

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Conflict of interest

A. Auricchio. Consultant: Biosense Webster, Boston Scientific, Medtronic, and Microport CRM; Intellectual property: Biosense Webster, Boston Scientific, and Microport CRM; Speaker fees: Boston Scientific, Medtronic, Microport CRM, and Philips.

All other authors have not reported conflict of interest.

CRediT authorship contribution statement

Rita Laureanti: Methodology, Software, Validation, Formal analysis, Writing - original draft, Visualization. **Giulio Conte:** Conceptualization, Methodology, Validation, Writing - review & editing. **Valentina D.A. Corino:** Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Visualization, Supervision. **Stefan Osswald:** Investigation, Resources, Data curation, Writing - review & editing, Project administration, Funding acquisition. **David Conen:** Investigation, Resources, Data curation, Writing - review & editing. **Laurent Roten:** Writing - review & editing. **Nicolas Rodondi:** Writing - review & editing. **Peter Ammann:** Writing - review & editing. **Christine S. Meyer-Zuern:** Writing - review & editing. **Leo Bonati:** Writing - review & editing. **Luca T. Mainardi:** Conceptualization, Methodology, Software, Writing - review & editing, Visualization, Supervision. **Angelo Auricchio:** Conceptualization, Methodology, Validation, Writing - review & editing, Visualization, Supervision.

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References

[1] S. Colilla, A. Crow, W. Petkun, D.E. Singer, T. Simon, X. Liu, Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population, Am. J. Cardiol. 112 (2013) 1142–1147, https://doi.org/10.1016/j.amjcard.2013.05.063.

[2] K.E. Odening, S. Deiß, D. Dilling-Boer, M. Didenko, U. Eriksson, S. Nedios, F.S. Ng, I. Roca Luque, P. Sanchez Borque, K. Vernooy, A.P. Wijnmaalen, H. Yorgun, Mechanisms of sex differences in atrial fibrillation: role of hormones and differences in electrophysiology, structure, function, and remodelling, EP Eur. 21 (2019) 366–376, https://doi.org/10.1093/europace/euy215.

[3] J. Friberg, H. Scharling, N. Gadsbøll, T. Truelsen, G.B. Jensen, Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (the Copenhagen City heart study), Am. J. Cardiol. 94 (2004) 889–894, https://doi.org/10.1016/j.amjcard.2004.06.023.

[4] A. Dhala, D. Underwood, R. Leman, E. Madu, D. Baugh, Y. Ozawa, Y. Kasamaki, Q. Xue, S. Reddy, Signal-averaged P-wave analysis of normal controls and patients with paroxysmal atrial fibrillation: a study in gender differences, age dependence, and reproducibility, Clin. Cardiol. 25 (2002) 525–531, https://doi.org/10.1002/clc.4960251109.

[5] D. Conen, N. Rodondi, A. Müller, J.H. Beer, A. Auricchio, P. Ammann, D. Hayoz, R. Kobza, G. Moschovitis, D. Shah, J. Schläpfer, J. Novak, M. Di Valentino, P. Erne, C. Sticherling, L.H. Bonati, G. Ehret, L. Roten, U. Fischer, A. Monsch, C. Stippich, J. Wuerfel, M. Schwenkglenks, M. Kühne, S. Osswald, Design of the Swiss Atrial Fibrillation Cohort Study (Swiss-AF): structural brain damage and cognitive decline among patients with atrial fibrillation, Swiss Med. Wkly. 147 (2017) https://doi.org/10.4414/smw.2017.14467.

[6] H. Calkins, G. Hindricks, R. Cappato, Y.-H. Kim, E.B. Saad, L. Aguinaga, J.G. Akar, V. Badhwar, J. Brugada, J. Camm, P.-S. Chen, S.-A. Chen, M.K. Chung, J.C. Nielsen, A.B. Curtis, D. Wyn Davies, J.D. Day, A. D'Avila, N.M.S. (Natasja) de Groot, L. Di Biase, M. Duytschaever, J.R. Edgerton, K.A. Ellenbogen, P.T. Ellinor, S. Ernst, G. Fenelon, E.P. Gerstenfeld, D.E. Haines, M. Haissaguerre, R.H. Helm, E. Hylek, W.M. Jackman, J. Jalife, J.M. Kalman, J. Kautzner, H. Kottkamp, K.H. Kuck, K. Kumagai, R. Lee, T. Lewalter, B.D. Lindsay, L. Macle, M. Mansour, F.E. Marchlinski, G.F. Michaud, H. Nakagawa, A. Natale, S. Nattel, K. Okumura, D. Packer, E. Pokushalov, M.R. Reynolds, P. Sanders, M. Scanavacca, R. Schilling, C. Tondo, H.-M. Tsao, A. Verma, D.J. Wilber, T. Yamane, 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary, EP Eur. 20 (2018) 157–208. doi:https://doi.org/10.1007/s10840-017-0277-z.

[7] J. Pan, W.J. Tompkins, A real-time QRS detection algorithm, IEEE Trans. Biomed. Eng. BME-32 (1985) 230–236, https://doi.org/10.1109/TBME.1985.325532.

[8] F. Censi, C. Ricci, G. Calcagnini, M. Triventi, R.P. Ricci, M. Santini, P. Bartolini, Time-domain and morphological analysis of the P-wave. Part I: technical aspects for automatic quantification of P-wave features, PACE - Pacing Clin. Electrophysiol. 31 (2008) 874–883, https://doi.org/10.1111/j.1540-8159.2008.01102.x.

[9] H.C. Bazett, An analysis of the time-relations of electrocardiograms, Ann. Noninvasive Electrocardiol. 2 (1997) 177–194, https://doi.org/10.1111/j.1542-474X.1997.tb00325.x.

[10] K. Ishida, H. Hayashi, A. Miyamoto, Y. Sugimoto, M. Ito, Y. Murakami, M. Horie, P wave and the development of atrial fibrillation, Hear. Rhythm. 7 (2010) 289–294, https://doi.org/10.1016/j.hrthm.2009.11.012.

[11] V.D.A. Corino, F. Censi, M. Tesoro, I. Corazza, E. Reggiani, G. Boriani, L.T. Mainardi, Beat-to-beat analysis of P waves in patient with atrial fibrillation history, Comput. Cardiol. (2010) 2016, pp. 685–688.

[12] G. Conte, M.L. Caputo, P.G.A. Volders, A. Luca, L. Mainardi, U. Schotten, V.D.A. Corino, F. Regoli, S. Zeemering, M. Zink, S. Yazdani, L. Kappenberger, T. Moccetti, J.M. Vesin, A. Auricchio, Concealed abnormal atrial phenotype in patients with Brugada syndrome and no history of atrial fibrillation, Int. J. Cardiol. 253 (2018) 66–70, https://doi.org/10.1016/j.ijcard.2017.09.214.

[13] I.T. Jolliffe, Principal Component Analysis, Second Edi, Springer, 2002. http://onlinelibrary.wiley.com/doi/10.1002/0470013192.bsa501/full.

[14] T. Taneja, B.W. Mahnert, R. Passman, J. Goldberger, A. Kadish, Effects of sex and age on electrocardiographic and cardiac electrophysiological properties in adults, PACE - Pacing Clin. Electrophysiol. 24 (2001) 16–21, https://doi.org/10.1046/j.1460-9592.2001.00016.x.

[15] U. Dogan, N.U. Dogan, A.O. Basarir, S. Yildirim, C. Celik, F. Incesu, K. Ozdemir, P-wave parameters and cardiac repolarization indices: does menopausal status matter? J. Cardiol. 60 (2012) 333–337, https://doi.org/10.1016/j.jjcc.2012.04.001.

[16] T. Karabag, V. Hanci, M. Aydin, S.M. Dogan, I.O. Turan, N. Yildirim, N.E. Gudul, Influence of menstrual cycle on P wave dispersion, Int. Heart J. 52 (2011) 23–26, https://doi.org/10.1536/ihj.52.23.

[17] N.I. Parikh, K. Kapphahn, H. Hedlin, J.E. Olgin, M.A. Allison, J.W. Magnani, K.R. Ryckman, M.E. Waring, M.V. Perez, B.V. Howard, Effects of reproductive period duration and number of pregnancies on midlife ECG indices: a secondary analysis from the Women's Health Initiative clinical trial, BMJ Open 8 (2018) 1–11, https://doi.org/10.1136/bmjopen-2017-019129.

[18] G. Salama, G.C.L. Bett, Sex differences in the mechanisms underlying long QT syndrome, AJP Hear. Circ. Physiol. 307 (2014) H640–H648, https://doi.org/10.1152/ajpheart.00864.2013.

[19] J.H. Burke, J.J. Goldberger, F.A. Ehlert, J.T. Kruse, M.A. Parker, A.H. Kadish, Gender differences in heart rate before and after autonomic blockade: evidence against an intrinsic gender effect, Am. J. Med. 100 (1996) 537–543, https://doi.org/10.1016/S0002-9343(96)00018-6.

[20] F. Beckers, B. Verheyden, A.E. Aubert, Aging and nonlinear heart rate control in a healthy population, Am. J. Physiol. Heart Circ. Physiol. 290 (2006) 2560–2570, https://doi.org/10.1152/ajpheart.00903.2005.

[21] P.W. Macfarlane, S.C. McLaughlin, B. Devine, T.F. Yang, Effects of age, sex, and race on ECG interval measurements, J. Electrocardiol. 27 (1994) 14–19, https://doi.org/10.1016/S0022-0736(94)80039-1.

[22] E. Simonson, H. Blackburn, T.C. Puchner, P. Eisenberg, F. Ribeiro, M. Meja, Sex differences in the electrocardiogram, Circulation. 22 (1960) 598–601. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=5600843.

[23] K. Hnatkova, P. Smetana, O. Toman, G. Schmidt, M. Malik, Sex and race differences in QRS duration, Europace. 18 (2016) 1842–1849, https://doi.org/10.1093/europace/euw065.
[24] N. Kumar, D. Saini, V. Froelicher, A gender-based analysis of high school athletes using computerized electrocardiogram measurements, PLoS One 8 (2013) https://doi.org/10.1371/journal.pone.0053365.
[25] J.B. Nielsen, J.T. Kühl, A. Pietersen, C. Graff, B. Lind, J.J. Struijk, M.S. Olesen, M.F. Sinner, T.N. Bachmann, S. Haunsø, B.G. Nordestgaard, P.T. Ellinor, J.H. Svendsen, K.F. Kofoed, L. Køber, A.G. Holst, P-wave duration and the risk of atrial fibrillation: results from the Copenhagen ECG study, Hear. Rhythm. 12 (2015) 1887–1895, https://doi.org/10.1016/j.hrthm.2015.04.026.
[26] G. Conte, A. Luca, S. Yazdani, M.L. Caputo, F. Regoli, T. Moccetti, L. Kappenberger, J.M. Vesin, A. Auricchio, Usefulness of P-wave duration and morphologic variability to identify patients prone to paroxysmal atrial fibrillation, Am. J. Cardiol. 119 (2017) 275–279, https://doi.org/10.1016/j.amjcard.2016.09.043.
[27] D. Filos, I. Chouvarda, D. Tachmatzidis, V. Vassilikos, N. Maglaveras, Beat-to-beat P-wave morphology as a predictor of paroxysmal atrial fibrillation, Comput. Methods Prog. Biomed. 151 (2017) 111–121, https://doi.org/10.1016/j.cmpb.2017.08.016.
[28] S. Pezzuto, A. Gharaviri, U. Schotten, M. Potse, G. Conte, M.L. Caputo, F. Regoli, R. Krause, A. Auricchio, Beat-to-beat P-wave morphological variability in patients with paroxysmal atrial fibrillation: an in silico study, Europace 20 (2018) iii26–iii35, https://doi.org/10.1016/0038-1098(79)91043-3.
[29] Z. Li, Z. Wang, Z. Yin, Y. Zhang, X. Xue, J. Han, Y. Zhu, J. Zhang, M.Y. Emmert, H. Wang, Gender differences in fibrosis remodeling in patients with long-standing persistent atrial fibrillation, Oncotarget. 8 (2017) 53714–53729, https://doi.org/10.18632/oncotarget.16342.
[30] T. Igarashi, S. Niwano, H. Fukaya, T. Yoshizawa, H. Nakamura, T. Fujiishi, N. Ishizue, J. Oikawa, J. Kishihara, M. Murakami, H. Niwano, J. Ako, Discrimination of paroxysmal and persistent atrial fibrillation in patients with new-onset atrial fibrillation, Int. Heart J. (2016) https://doi.org/10.1536/ihj.15-476.
[31] M.F. El-Chami, C. Brancato, J. Langberg, D.B. Delurgio, H. Bush, L. Brosius, A.R. Leon, QRS duration is associated with atrial fibrillation in patients with left ventricular dysfunction, Clin. Cardiol. 33 (2010) 132–138, https://doi.org/10.1002/clc.20714.
[32] M.C. Mandyam, E.Z. Soliman, A. Alonso, T.A. Dewland, S.R. Heckbert, E. Vittinghoff, S.R. Cummings, P.T. Ellinor, B.R. Chaitman, K. Stocke, W.B. Applegate, D.E. Arking, J. Butler, L.R. Loehr, J.W. Magnani, R.A. Murphy, S. Satterfield, A.B. Newman, G.M. Marcus, The QT interval and risk of incident atrial fibrillation, Hear. Rhythm. 10 (2013) 1562–1568, https://doi.org/10.1016/j.hrthm.2013.07.023.
[33] S. Mandic, H. Fonda, F. Dewey, V. Van Le, R. Stein, M. Wheeler, E.A. Ashley, J. Myers, V.F. Froelicher, Effect of Gender on computerized electrocardiogram measurements in college athletes, Phys. Sportsmed. 38 (2010) 156–164.
[34] J.B. Nielsen, A. Pietersen, C. Graff, B. Lind, J.J. Struijk, M.S. Olesen, S. Haunsø, T.A. Gerds, P.T. Ellinor, L. Køber, J.H. Svendsen, A.G. Holst, Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG study, Hear. Rhythm. 10 (2013) 1249–1256, https://doi.org/10.1016/j.hrthm.2013.04.012.

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