Initial Reference Values of Electrocardiographic Alternans by Enhanced Adaptive Matched Filter

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Abstract

*Electrocardiographic alternans (ECGA) is the ABAB fluctuation of the electrocardiogram (ECG) and may manifest as P-wave/QRS-complex/T-wave alternans (PWA/QRSA/TWA). ECGA is a cardiovascular risk index, and its characterization may depend on the automatic identification method. Normal ranges (needed to define risk conditions) are still not available for the new enhanced adaptive matched filter (EAMF) method. Thus, the present study aims to provide them. EAMF was used to characterize ECGA (in terms of: amplitude, μV; area, μV×ms; and duration, number of beats) in 15-lead ECG from 52 healthy subjects (39/13 male/female), from the "PTB Diagnostic ECG Database". Median ECGA values over leads and subjects were: 2 μV, 200 μV×ms, and 17 beats for PWA; 1 μV, 80 μV×ms, and 8 beats for QRSA; and 7 μV, 1300 μV×ms, and 49 beats for TWA. ECGA in females (PWA: 4 μV, 350 μV×ms, and 22 beats; QRSA: 1 μV, 80 μV×ms, and 11 beats; TWA: 10 μV; 2000 μV×ms, and 49 beats) was higher (*p<0.05) than ECGA in males (PWA: 2 μV*, 200 μV×ms*, and 16 beats*; QRSA: 1 μV, 80 μV×ms, and 7 beats; TWA: 6 μV, 1150 μV×ms, and 48 beats). Maximum ECGA values were observed in fundamental leads. The observed reference ECGA values seem reliable if comparing with pathological populations but are initial and analysis of wider datasets is needed.*

1. Introduction

When one of the waves of the electrocardiogram (ECG) fluctuates according to an ABAB pattern, ECG alternans (ECGA) is manifesting [1]. ECGA may appear on the ECG as P-wave alternans (PWA), QRS-complex alternans (QRSA) and T-wave alternans (TWA) [2-4]. The phenomenon physiological origin is complex and not univocal. Some speculate that its origin may lay on high heterogeneity in cardiac tissue and/or voltage-dependent mechanisms and/or calcium-dependent mechanisms [5-7]. In clinical applications, ECGA acts as cardiovascular risk index of arrhythmia predisposition [2-4]. Indeed, it is associated with a wide variety of cardiac pathologies affecting both atria and ventricles, and it is able to predict malignant arrhythmias and sudden cardiac death [8].

All the existent ECGA automatic identification methods are implemented to detect and quantify only TWA, except for one: the enhanced adaptive match filter (EAMF) method [1]. In this context, ECGA (and especially TWA) measurements may depend on the automatic method used to identify it. Each method has its own implicit definition of TWA and basing on it, the method performs a different quantification and characterization of ECGA [9]. If the methodological approach is to interpret ECGA phenomenon as a continuous rather than on-off (*i.e.*, present or not present) phenomenon, it is possible to quantify ECGA levels even on the ECG of healthy people, with a non-null magnitude but lower than pathological one. This means that there is a range of ECGA values that can be considered as normal and can serve as reference values in assessing the risk condition. In fact, the role of a cardiovascular index, such as the ECGA, in identifying the risk condition, is subject to the definition of the reference range, so if the risk index is within it the risk is low, otherwise the risk increases. Furthermore, the literature shows that there are some differences in cardiac (and ECG, as a consequence) characteristics between female and male population [10-12]. This makes the investigation of female and male reference values for risk indexes definition necessary. This distinction also applies for TWA [13] and more in general for ECGA.

Normal reference values for the recently proposed EAMF method are not available yet. Thus, the present study aims to provide initial reference ECGA values to compare with in future studies on pathological subjects, by analyzing ECGA in a healthy population, also discriminating between male and female population.

2. Clinical data

ECGA was detected and characterized in healthy subjects' ECG belonging to the "PTB Diagnostic ECG Database", freely available on PhysioNet [14-15]. The database contains raw ECG recordings acquired from 52 healthy subjects, of whom 39 are male and 13 are female.

Overall, the healthy population is 43±16 years old (male: 42±14 years old; female: 48±19 years old). ECG acquisitions were noninvasively performed and composed by both the conventional 12 standard leads (fundamental leads (I, II, III); augmented leads (aVR, aVL, aVF); precordial leads (V1, V2, V3, V4, V5, V6)), and the 3 Frank leads (Vx, Vy, Vz). ECG tracings were digitized at 1000 Hz, with 16-bit resolution, 2-min long and recorded while the subjects were in resting condition [14].

3. Analysis by the enhanced adaptive matched filter method and statistics

ECGA analysis procedure was performed on each available ECG lead. Identification of PWA, QRSA, and TWA was performed by the EAMF method [1]. Its application involves an initial preprocessing phase and an alternans detection and characterization phase.

The preprocessing phase includes resampling to 200 Hz, band-pass filtering between 0.1 Hz and 35 Hz, and subtraction of the baseline. Filtering is performed using a 6^{th} order bidirectional Butterworth filter and baseline was estimated by cubic spline interpolation of fiducial points in PR-segment. Then, after R-peak detection (through a procedure based on Pan-Tompkins' algorithm) RR intervals are computed, and heartbeat fiducial points (Q-wave onset, Qon; QRS-complex end, J; P-wave onset, Pon; T-wave end, Tend) are detected [1]. Experimental and RR-dependent formulas were used: Qon = R − 50 ms; J = R + 50 ms; if mRR < 600 ms, Pon = Qon − 180 ms and Tend = R + 60 ms + 0.35·$\sqrt{mRR}$; if 600 ms ≤ mRR < 1100 ms, Pon = Qon − 200 ms and Tend = R + 100 ms + 0.4·$\sqrt{mRR}$; if $mRR \geq$ 1100 ms, Pon = Qon − 250 ms and Tend = R + 150 ms + 0.45·$\sqrt{mRR}$ (where mRR is mean RR and R is R peak). These fiducial points define three heartbeat sections: the P section (from Pon to Qon), the QRS section (from Qon to J), and the T section (from J to Tend). The theoretical approach of EAMF method grounds on two suitability criteria: the first criterium is met if RR standard deviation do not exceed 10% of mean RR; the second criterium is met if at least 90% of the QRS complexes and T waves have a very strong correlation (0.85 or greater) with QRS complex and T wave of the template heartbeat (median over all heartbeats), respectively. If both criteria are met, low-correlating heartbeats are replaced by the template and ECG tracing undergoes the alternans detection phase.

ECGA detection was performed in parallel among ECGA kinds and starts with the ECG tracing enhancement. It consists in laying down to baseline all heartbeat sections except for the one on which alternans is being detected. Thus, three signals were determined: P, QRS, and T signals if P, QRS, and T sections are the only ones to be preserved, respectively. Then, these signals are filtered in a very narrow frequency band around ECGA frequency (defined as half heart rate). Filtering is performed implementing a 6^{th} order bidirectional Butterworth filter, having cut-off frequencies 0.06 Hz before and after ECGA frequency. Thus, if the P (or QRS or T) section is fluctuating the filter output is a pseudo-sinusoid with maxima/minima on the P (or QRS or T) section. ECGA feature extraction was performed to characterize it in terms of amplitude (Am, μV; difference between corresponding pseudo-sinusoid maxima and minima), area (Ar, μV×ms; product of ECGA amplitude by the duration of the wave of interest) and duration (D, adi; number of fluctuating heartbeats), considering only the 64 central heartbeats of the ECG tracing.

Distributions of PWA/QRSA/TWA amplitudes, areas and durations for each ECG lead, as well as of RR interval, were considered over the general, male and female populations. Each of them was tested for normality by the Lilliefors test. If one (or more) distribution turned out to be not normal, all distributions were characterized in terms of median and interquartile range (IR, difference between the 75^{th} and 25^{th} percentiles). Otherwise, they were characterized in terms of mean and standard deviation. Moreover, for each ECGA feature, median values over leads were computed for each subject. These distributions (considered as total) were characterized as median [IR] over subjects and the ones related to males and females were compared to verify statistical difference through Wilcoxon rank-sum test, setting statistical significance (p) at 0.05.

4. Results

ECG lead distributions of ECGA features (*i.e.*, Am, Ar and D) for the general, male and female populations were characterized in terms of median[IR] in tables 1, 2 and 3, respectively, since not all of them resulted to be normal. Female ECGA was higher than male ECGA, but statistical significance was reached only for PWA. Eventually, median[IR] RR interval for the general, male and female populations were: 889[205] ms; 889 [200] ms; 878[257] ms, respectively.

5. Discussion and conclusion

The new EAMF method quits for the first time the traditional restrictive assumption of existence of only TWA. Thanks to the enhancement phase that allows to avoid reciprocal influence among possible different concurrent ECGA manifestations, it performs reliably in ECGA characterization [1]. Thus, it may be used in clinical applications to identify subjects at higher risk to develop possibly dangerous arrhythmias. Basing on the assumption of alternans phenomenon as continuous [8], reference ECGA ranges are needed to accomplish this role. Indeed, this study confirmed that low levels of

Table 1. ECGA lead distributions in the general population expressed as median[IR].

Lead	PWA			QRSA			TWA		
	Am (μV)	Ar (μV×ms)	D (adi)	Am (μV)	Ar (μV×ms)	D (adi)	Am (μV)	Ar (μV×ms)	D (adi)
I	2 [5]	200 [500]	21 [31]	1 [4]	80 [320]	9 [24]	6 [6]	1100 [1200]	47 [15]
II	5 [6]	500 [600]	31 [25]	3 [4]	200 [320]	14 [23]	11 [11]	2200 [2200]	51 [10]
III	3 [4]	300 [400]	24 [22]	2 [1]	160 [80]	13 [15]	9 [8]	1700 [1600]	47 [13]
aVR	3 [7]	300 [700]	23 [27]	1 [4]	80 [320]	10 [23]	8 [6]	1500 [1200]	47 [11]
aVL	2 [5]	200 [475]	13 [23]	1 [2]	80 [160]	5 [15]	6 [7]	1200 [1400]	46 [13]
aVF	3 [5]	300 [500]	23 [24]	1 [2]	80 [160]	11 [19]	9 [8]	1800 [1600]	49 [13]
V1	1 [3]	100 [250]	12 [18]	1 [2]	80 [160]	7 [14]	7 [6]	1300 [1200]	47 [13]
V2	2 [3]	200 [300]	15 [24]	2 [3]	160 [240]	17 [21]	9 [6]	1800 [1200]	49 [13]
V3	2 [3]	200 [300]	16 [22]	2 [3]	160 [240]	14 [21]	7 [7]	1400 [1400]	47 [11]
V4	2 [3]	200 [300]	18 [18]	1 [2]	80 [160]	11 [12]	7 [8]	1400 [1650]	49 [11]
V5	2 [2]	200 [200]	19 [18]	1 [3]	80 [240]	9 [13]	7 [7]	1400 [1500]	46 [14]
V6	2 [3]	200 [300]	18 [18]	1 [2]	80 [180]	6 [17]	6 [9]	1200 [1800]	47 [14]
Vx	1 [2]	100 [200]	7 [20]	1 [2]	80 [160]	6 [14]	4 [5]	800 [1000]	42 [13]
Vy	2 [2]	200 [200]	16 [20]	1 [2]	80 [160]	7 [11]	6 [6]	1200 [1200]	45 [13]
Vz	0 [1]	0 [100]	0 [7]	0 [0]	0 [0]	0 [4]	3 [3]	600 [600]	37 [19]
Tot	**2 [3]**	**200 [300]**	**17 [17]**	**1 [2]**	**80 [160]**	**8 [15]**	**7 [7]**	**1300 [1400]**	**49 [9]**

ECGA can be observed in healthy subjects, so are physiological. The observed values showed to be reliable, since they are often statistically lower than corresponding ECGA values observed in pathological subjects [16].

Moreover, it endorses the lead and gender dependence of ECGA. Different values were obtained among analyzed leads and maximum values of ECGA features were observed in the fundamental leads. ECGA values were always higher in the female population than in the male one, although only the alternans relating to atrial depolarization showed statistically significant differences. All the subjects considered were at rest during ECG acquisition (and this is confirmed by the heart rate values), so it was not possible to analyze the behavior of the ECGA in relation to the different activity conditions of the subject. Given the dependence of the ECGA on heart rate [8], the comparison of the values observed here with the pathological ones should be made at a comparable heart rate. Moreover, wide ECGA IR suggest a high variability among subjects. This can be due to different non-pathological subjects' conditions, as age.

In conclusion, the reference ECGA values for EAMF method observed here can be read as reliable, but preliminary. Future studies should consider larger populations possibly confirming the findings of this work and also including age and heart rate stratification.

Table 2. ECGA lead distributions in the male population expressed as median[IR].

Lead	PWA			QRSA			TWA		
	Am (μV)	Ar (μV×ms)	D (adi)	Am (μV)	Ar (μV×ms)	D (adi)	Am (μV)	Ar (μV×ms)	D (adi)
I	1[3]	100[300]	13[28]	1[2]	80[160]	5[18]	5[5]	1000[1000]	42[17]
II	4[5]	350[500]	25[25]	2[4]	120[320]	12[24]	9[10]	1800[2000]	50[13]
III	3[3]	250[300]	19[19]	2[1]	160[80]	13[11]	7[9]	1400[1800]	46[15]
aVR	2[3]	200[300]	19[23]	1[2]	80[160]	6[16]	6[5]	1200[1000]	46[10]
aVL	2[5]	200[450]	13[23]	1[2]	80[160]	5[15]	6[8]	1200[1600]	45[14]
aVF	2[4]	200[400]	22[24]	2[2]	120[160]	11[15]	7[9]	1400[1800]	50[13]
V1	1[3]	100[300]	12[18]	1[2]	80[160]	6[13]	6[7]	1200[1400]	45[14]
V2	2[3]	200[300]	15[25]	2[3]	160[240]	16[18]	8[6]	1500[1200]	49[13]
V3	2[4]	200[400]	13[21]	2[4]	160[320]	16[22]	7[7]	1400[1400]	48[12]
V4	2[2]	200[200]	15[17]	2[2]	120[160]	11[13]	6[9]	1200[1800]	50[11]
V5	2[2]	200[200]	15[19]	2[2]	120[160]	12[11]	6[9]	1100[1800]	46[14]
V6	2[3]	200[300]	15[21]	1[2]	80[160]	6[17]	5[9]	1000[1800]	47[15]
Vx	1[2]	100[200]	7[16]	1[2]	80[160]	6[14]	4[5]	800[1000]	41[16]
Vy	1[3]	100[300]	13[18]	1[1]	80[80]	7[10]	6[6]	1200[1200]	45[13]
Vz	0[1]	0[100]	0[6]	0[0]	0[0]	0[3]	3[3]	600[650]	37[19]
Tot	**2[2]**	**200[200]**	**16[17]**	**1[2]**	**80[160]**	**7[14]**	**6[7]**	**1150[1400]**	**48[10]**

Table 3. ECGA lead distributions in the female population expressed as median[IR] (*: p<0.05).

Lead	PWA			QRSA			TWA		
	Am (μV)	Ar (μV×ms)	D (adi)	Am (μV)	Ar (μV×ms)	D (adi)	Am (μV)	Ar (μV×ms)	D (adi)
I	5[9]	500[900]	35[17]	7[5]	520[400]	31[13]	12[11]	2300[2200]	52[6]
II	8[6]	800[550]	38[21]	5[6]	400[440]	28[23]	15[11]	2900[2100]	52[11]
III	5[4]	500[400]	29[19]	1[2]	80[160]	9[21]	10[6]	2000[1100]	53[8]
aVR	5[7]	450[700]	33[18]	5[5]	360[400]	24[16]	10[12]	1900[2400]	47[12]
aVL	2[5]	200[475]	18[23]	1[2]	80[160]	6[14]	7[5]	1400[950]	48[4]
aVF	7[4]	700[400]	40[16]	1[3]	40[240]	5[20]	13[5]	2600[900]	48[11]
V1	2[3]	150[300]	16[21]	1[2]	80[160]	10[19]	9[5]	1700[1000]	50[4]
V2	3[4]	250[400]	15[24]	3[3]	240[240]	19[25]	11[3]	2100[600]	51[7]
V3	3[5]	300[475]	27[16]	1[3]	80[220]	8[18]	11[4]	2200[750]	47[11]
V4	3[3]	300[300]	21[19]	1[2]	80[140]	13[11]	10[4]	2000[800]	48[8]
V5	3[2]	300[175]	21[10]	1[3]	80[240]	8[19]	9[4]	1800[750]	49[9]
V6	2[4]	200[425]	21[27]	1[4]	80[280]	6[27]	8[4]	1600[750]	50[6]
Vx	1[4]	100[425]	7[32]	0[3]	0[220]	0[14]	4[6]	800[1100]	46[8]
Vy	4[4]	350[400]	22[26]	1[3]	80[200]	11[24]	6[5]	1200[1000]	44[14]
Vz	0[2]	0[200]	0[16]	0[1]	0[80]	0[6]	3[3]	500[600]	35[17]
Tot	**4*[4]**	**350*[375]**	**22*[16]**	**1[3]**	**80[240]**	**11[26]**	**10[5]**	**2000[950]**	**49[4]**

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