The Signal-Averaged Electrocardiograms to Atrial Activation in Patients With and Without Paroxysmal Atrial Fibrillation

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Objective: To analyze the parameters of the time domain P-wave signal-averaged electrocardiogram (P-SAECG) and compare them with the P-wave duration on the conventional electrocardiogram (P on ECG) as well as the left atrium diameter (LAD) and left ventricular ejection fraction (EF) obtained on the echocardiogram in order to evaluate patients with paroxysmal atrial fibrillation (PAF).

Methods: One hundred and eighty-one patients were included in the study: 117 with confirmed PAF and 64 without PAF. The P-SAECG parameters used were: the filtered P-wave duration (FPD), the root mean square (RMS) voltages in the last 40, 30 and 20 ms of the filtered P-wave (RMS 40, RMS 30 and RMS 20), the root mean square voltage of the filtered P-wave potentials (RMS P), the integral of the potentials during the filtered P-wave (Integral P) and the filtered P-wave late potential durations below 3 mV (PL<3).

Results: The parameters that presented significant statistical differences between the groups were: FPD, RMS 40, 30 and 20, PL<3, P on ECG and LAD. The ROC curve calculations demonstrated the best cut-off points and performance estimates for each parameter: sensitivity, specificity, area under the curve and p-value (p).

Conclusion: The time domain P-SAECG proved to be a superior method to identify patients with paroxysmal atrial fibrillation than the conventional electrocardiogram and echocardiogram.

Key words: P-wave signal averaged electrocardiogram, atrial activation, paroxysmal atrial fibrillation.

Scientific studies have demonstrated that atrial late potentials are directly related to the development of atrial fibrillation[1-4]. Late potentials are low amplitude, high frequency electrical signals at the end of atrial activation, generated by delayed and fragmented conduction and can only be recorded with a P-wave signal averaged electrocardiogram (P-SAECG).

The objective of this study was to analyze the time domain P-SAECG parameters and compare them to the duration of the longest P-wave on the conventional electrocardiogram (ECG), the left atrium diameter and the left ventricular ejection fraction obtained on the echocardiogram for patients with or without paroxysmal atrial fibrillation (PAF).

Methods

One hundred and eighty-one patients were included in the study, classified in two groups. Group I consisted of 117 patients of which 73 were males and 44 were females between the ages of 18 and 85, mean 57.50 years ± 15.13, with confirmed PAF, with or without structural cardiopathies. Group II consisted of 64 patients, of which 40 were males, between the ages of 23 and 83, mean 55.47 years ± 16.34, without PAF.

At the time of the P-SAECG, 79.5% of the patients in group I (with PAF) and 26.6% of the patients in group II (without PAF) were taking antiarrhythmic medication.

The specific method used in the study was the P-SAECG, in order to identify and quantify low amplitude, high frequency electrical potentials at the end of the P-wave which are known as atrial late potentials and indicate delayed, fragmented conduction at the end of atrial depolarization which is an arrhythmogenic substrate for atrial fibrillation.

The recording of the micro-volt size electrical potentials is accomplished using the signal averaging technique in which the noise level is inversely proportional to the number of signals detected. The P-SAECG triggered by the P-waves eliminates the effect of ectopic atrial beats and variations in the PR interval.

The Marquette Medical Systems' Signal-Averaged High Resolution P-wave (P Hi-Res) machine was used. This machine detects P waves that are correlated to a standard P-wave and

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only those with a correlation of 95% or more are accepted and averaged. The alignment and averaging continues for a target number of beats, for example 250, or preferably until a targeted level of minimal electrical interference (less than 1 μV) is reached.

The P-waves from the orthogonal X, Y and Z leads are combined in a spatial result called vector magnitude (VM) – using the formula VM= $\sqrt{X^2 + Y^2 + Z^2}$ – that is amplified and filtered using the following criteria: on the vertical axis 1 mm = 1μV and on the horizontal axis 1 mm = 5 ms. The machine automatically positions the cursors that mark the start and end of the P-wave in the amplified result for the three leads, rarely requiring manual adjustments. When adjustments were required they were made by two researchers who had reached a consensus. The start and end of the P-wave were defined as signals with a continuous level of 1 μV.

The P-SAECG parameters are measured instantly and automatically by the machine in VM, with the exception of the P-wave late potential duration below 3μV (PL< 3) parameter which was manually measured by two observers in order to establish consensus.

The conventional ECG was recorded using the Hewlett-Packard HP 708 electrocardiograph with a 0.5 Hz - 40 Hz filter, velocity of 25 mm/s (1 mm = 40 ms) and calibration of 10 mm/mV. The ECG P-wave duration measurement was verified using a magnifying glass for all leads and the longest was chosen.

Either the HDI 3000 or HDI 5000 Philips Ultrasound echocardiogram (ECHO) machines were used. The left atrium diameter was measured with a two-dimensional guided M-mode echocardiography using the parasternal long axis view during the final stage of the ventricular systole in accordance with the recommendations of the American Society of Echocardiography. The left ventricular ejection fraction was measured using Teichholz.

The patients were evaluated during sinus rhythm using the P-SAECG, ECG and ECHO for the following ten study parameters:

During the P-SAECG – 1) FPD = filtered P-wave duration (in ms). 2) RMS 40 = root mean square voltage of the potentials in the last 40 ms of the filtered P-wave (in μV). 3) RMS 30 = root mean square voltage of the potentials in the last 30 ms of the filtered P-wave (in μV). 4) RMS 20 = root mean square voltage of the potentials in the last 20 ms of the filtered P-wave (in μV). 5) RMS P = root mean square voltage of the filtered P-wave potentials (in μV). 6) Integral P = integral of the potentials during the filtered P-wave (in μV.s). 7) PL < 3 = filtered P-wave late potential durations less than 3 μV (retrograde measurement from the end of the P-wave in ms).

During the ECG – 8) P on ECG = duration of the longest P-wave on the conventional ECG (in ms).

During the ECHO – 9) LAD = left atrium diameter (in mm). 10) EF = left ventricular ejection fraction (in ejection fraction units).

Statistical treatment - The analysis was divided into four stages:

Stage 1 - Descriptive statistics and tests to determine whether or not the study variable results presented a normal distribution pattern, using the following tests: Boxplot and Cook's Distance tests to identify extreme values (outliers); Kolmogorov-Smirnov with Lilliefors correction to analyze sample normality and the Normal Q-Q Plot for residual and sample normality analyses;

Stage 2 - Post analysis descriptive statistics of variable normality and exclusion of extreme values (outliers), analysis of study variables (P-SAECG, ECG and ECHO parameters) and estimation of confidence intervals (95%);

Stage 3 - Hypothesis testing. The main hypothesis tested in this study was the detection of differences in the study parameters between patients with and without PAF. Nevertheless, knowing that there are various factors that can interfere or even interact in result behavior and the difficulty to control the factors that cause these interferences, we opted to control the factors of age, gender, left atrium diameter and use of antiarrhythmics in order to verify any possible interactions of these factors with the groups. In the model adopted, age and LAD were used as co-variables and the factors gender and use of antiarrhythmics, were employed in the interaction analysis with the factor group. Variance analysis was performed using Simple Factorial Anova for the variables in which the presumption of sample normality was accepted. The Mann-Whitney test was used for the variables in which the presumption of sample normality was not accepted. In this case, only the hypothesis of difference between the groups was tested, there was no association with any other co-variable model or even interaction verification between the factors;

Stage 4 - In order to analyze the performance estimates for the parameters that presented significant differences between groups I and II, the ROC curve was adopted to determine the cut-off point between the normal and abnormal result standards which also supplied the sensitivity, specificity, area under the curve and p-value data for each parameter.

Results

The results found in groups I and II, for each parameter are shown in table 1 and were expressed as: average, standard deviation, minimum value, maximum value and p-value.

The parameters that presented significant statistical differences between groups I and II were: FDP, RMS 40, RMS 30, RMS 20, PL<3, P on ECG and LAD. The parameters RMS P, Integral P and EF did not present any significant differences between the groups.

Variance analysis did not confirm any interaction between the factors of antiarrhythmic use or patient gender, or the co-variables age and LAD with the factor group for any of the study parameters indicating that these factors should be treated and analyzed separately as they do not cause any significant effect when studied on a group basis.

In reference to the factor of use of antiarrhythmics, a significant statistical difference was only detected for the parameter FPD. The gender factor only demonstrated a significant difference for the parameter PL<3. The co-variables

age and LAD only presented significant differences for the LAD and FPD parameters.

To calculate the method performance estimates – that are sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) – a standardized method was used to determine the cut-off points for each parameter, equivalent to the arithmetic average between the upper and lower limits of the 95% confidence intervals for the average study values in the groups with and without PAF.

The cut-off points obtained were: FPD ≥ 130.40 ms; RMS 40 ≤ 5.67 μV; RMS 30 ≤ 4.81 μV; RMS 20 ≤ 4.40 μV; PL<3 ≥ 10.61 ms; P on ECG ≥ 89.75 ms; and LAD ≥ 36.45 mm, as shown in table 2.

Discussion

Comparison of the values obtained in this study for the ten parameters between the groups I and II, demonstrated that in group I the parameters that include time measurements (FPD, Integral P, PL<3 and P on ECG) or size (LAD) were higher and the parameters that measure voltages (RMS 40, RMS 30, RMS 20 and RMS P) were lower. EF was almost the same for both groups suggesting that the left ventricular ejection fraction has no influence on PAF.

Calculation of the p-value (≤ 5%) revealed significant statistical differences between groups I and II for the parameters: FPD, RMS 40, RMS 30, RMS 20, PL<3, P on ECG and LAD. The parameters RMS P, Integral P and EF did not present any significant differences between the groups.

Note also that LAD significantly influenced FPD, confirming that left atrium dilation is a factor that increases this parameter.

In the calculation of performance estimates for the parameters using the confidence interval of the averages, it was noted that the most sensitive parameter to distinguish differences between the patients with and without PAF was FPD (72.65%), and P on ECG was the least sensitive (33.33%). P on the ECG had the highest specificity (98.44%), and RMS 20 had the lowest specificity (50%).

The most influential parameters for the four combined performance estimates to identify cases with and without PAF were: FDP and PL<3.

Using the ROC curve, the best parameter to differentiate the groups with and without PAF was FDP (0.83), followed by P on ECG (0.72), LAD (0.69), PL<3 (0.67), RMS 40 (0.39), RMS 30 (0.37) and RMS 20 (0.35), as shown in table 3.

Parameter	Group	AVG	SD	Min.	Max.	p
P Duration	With PAF	139.79	16.63	104.00	196.00	
	W/O PAF	121.36	10.77	95.00	144.00	0.000*
RMS 40	With PAF	5.26	2.15	2.00	11.00	
	W/O PAF	6.23	2.27	3.00	12.00	0.005*
RMS 30	With PAF	4.40	2.00	1.00	9.00	
	W/O PAF	5.33	1.97	2.00	11.00	0.003*
RMS 20	With PAF	3.95	1.89	1.00	9.00	
	W/O PAF	4.97	1.94	2.00	10.00	0.001*
RMS P	With PAF	6.91	2.33	3.00	13.00	
	W/O PAF	7.09	2.02	4.00	13.00	0.588
Integral P	With PAF	728.40	267.68	256.00	1,529.00	
	W/O PAF	672.47	210.75	318.00	1,300.00	0.150
PL<3	With PAF	14.70	10.29	0.00	40.00	
	W/O PAF	7.58	3.23	0.00	15.00	0.000*
P on ECG	With PAF	100.00	20.00	80.00	160.00	
	W/O PAF	80.00	10.00	60.00	120.00	0.000*
LAD	With PAF	38.30	5.71	26.00	53.00	
	W/O PAF	34.70	3.82	27.00	44.00	0.000*
EF	With PAF	0.69	0.10	0.32	0.83	
	W/O PAF	0.68	0.11	0.32	0.81	0.603

On the P-SAECG: FPD = *filtered P-wave duration;* RMS 40, 30, 20 = *root mean square voltages of the potentials in the last 40, 30, 20 ms of the filtered P-wave;* RMS P = *root mean square voltage of the filtered P-wave potentials; integral* P= *integral of the potentials during the filtered P-wave;* PL<3 = *filtered P-wave late potential durations below 3 μV. On the conventional electrocardiogram:* P *on* ECG = *duration of the longest P-wave on the conventional electrocardiogram. On the echocardiogram:* LAD = *left atrium diameter;* EF = *left ventricular ejection fraction.* SD = *standard deviation;* p = *p-value;* PAF = *paroxysmal atrial fibrillation;* * = *significant statistical difference.;* AVG = *average;* MIN = *minimum;* MAX = *maximum;* W/O = *without.*

Table 1 - Descriptive statistics of the parameters in groups I (with PAF) and II (without PAF)

A pioneer study on the P-SAECG to identify patients at risk for developing PAF[2] proposed the recording of P-SAECG signals triggered by the P-waves rather than the QRS complexes. High-pass filters of 40 Hz and low-pass filters of 300 Hz were used to study the following parameters: FPD (filtered P-wave duration), RMS 10, RMS 20 and RMS 30 (root mean square voltages of the potentials in the last 10, 20 or 30 ms of the filtered P-wave spatial magnitude).

The parameters FPD, RMS 10 and RMS 20 showed significant statistical differences between the groups with and without PAF, and the respective values found were: FPD = 137.0 ± 14.3 and 118.6 ± 11.3 ms, $p < 0.001$; RMS 10 = 1.92 ± 0.58 and 2.49 ± 0.78 μV, $p < 0.001$; RMS 20 = 2.47 ± 0.78 and 3.46 ± 1.20 μV, $p < 0.001$. RMS 30 did not reveal any difference between the groups.

Other studies, which used the same methods as ours, revealed similar results in relation to FPD and RMS 20. However, in our study RMS 30 also revealed differences between the groups and the RMS 10 parameter was not analyzed.

In 1995, other authors[4] reported that the best criteria to distinguish patients with and without PAF would be PL<3 (filtered P-wave late potential durations below 3 μV). They verified that PL<5 would not be a relevant criterium to confirm the presence of late potentials as in the cases with small amplitude P-waves (6 to 7 μV), PL<5 would present normal segments. Furthermore, PL<2 could present false results, since the end of the P-wave is defined as the return of the atrial signal to the baseline below 1μV and therefore a limit of 2 μV would cause overlaps in the values for the groups with and without PAF. The parameter PL<3 presented an average value of 24.7 ± 8.4 ms for the group with PAF and by adopting the value > 15 ms as abnormal, obtained sensitivity and specificity of 100%. The parameters RMS 20 and FPD also presented significant differences between the groups; however by adopting FPD > 120 ms, they found sensitivity and specificity of 85%.

In our study, PL<3 with a cut-off point of 10.61 ms revealed sensitivity of 52.14%, specificity of 87.10%, positive predictive value of 88.41% and negative predictive value of 49.09%. Using the cut-off point of 15 ms recommended by Gondo et al[4], we found specificity of 100%, similar to their findings, but sensitivity of only 40.17%.

The explanation for this difference is that in the present study, the end of the P-wave was considered as being the return of the atrial signal to the baseline below 1 μV; different from that used by Gondo et al[4].

Another observation is that in our case study, patients who had presented a single episode of PAF were included while those authors only admitted patients with more than one episode and a duration greater than 30 seconds.

Yamada's colleagues[5] analyzed 132 healthy patients (66 of each gender), with ages between fourteen and eighty years – average of 38 ± 17 years, using the same signal acquisition method and filter described earlier (similar to the present study), and found FPD values of 118 ± 10 ms and RMS 20 values of 3.2 ± 0.9 μV (similar to our study). Using the ninetieth percentile, P-SAECG was defined as abnormal when FPD was > 132 ms and RMS 20 was < 2.3 μV. From the case study of 132 people without PAF or cardiopathies,

Parameter	G	AVG	CI 95 %		CUT-OFF	S (%)	SP (%)	PPV (%)	NPV (%)
			Lower	Upper					
FPD	I	139.79	136.75	142.84	≥ 130.40	72.65	82.81	88.54	62.35
	II	121.36	118.67	124.05					
RMS 40	I	5.26	4.86	5.66	≤ 5.67	62.28	53.13	70.30	44.16
	II	6.23	5.67	6.80					
RMS 30	I	4.40	4.04	4.77	≤ 4.81	43.59	60.94	67.11	37.14
	II	5.33	4.84	5.82					
RMS 20	I	3.95	3.60	4.30	≤ 4.40	68.38	50.00	71.43	46.38
	II	4.97	4.49	5.45					
PL<3	I	14.70	12.82	16.59	≥ 10.61	52.14	87.10	88.41	49.09
	II	7.58	6.76	8.40					
P on ECG	I	97.90	94.40	101.30	≥ 89.75	33.33	98.44	97.50	44.68
	II	82.80	80.50	85.10					
LAD	I	38.30	37.24	39.35	≥ 36.45	56.97	71.88	79.31	48.94
	II	34.70	33.74	35.66					

G = Group; I = Group with PAF; II = Group without PAF; AVG = *Average;* CI = *Confidence interval;* S = *Sensitivity;* SP = *Specificity;* PPV = *Positive predictive value;* NPV = *Negative predictive value. On the P-SAECG:* FPD= *Filtered P-wave duration;* RMS *40, 30, 20 = Root mean square voltage of the potentials in the last 40, 30, 20 ms of the filtered* P-wave; PL<3= *Filtered* P-wave *late potential durations below 3 μV. On the conventional* ECG: P *on* ECG *= Duration of the longest* P-wave *on the conventional electrocardiogram. On the echocardiogram:* LAD = *Left atrium diameter.*

Table 2 - Performance estimates using the confidence interval

Parameter	CP	S %	SP %	AUC %	P
FPD	131.50 ms	73	86	0.83	< 0.0001
RMS 40	5.50 μV	39	47	0.39	< 0.01
RMS 30	4.50 μV	44	40	0.37	< 0.04
RMS 20	4.50 μV	32	50	0.35	< 0.001
PL < 3	9.00 ms	62	68	0.67	< 0.0001
P on ECG	90.00 ms	54	85	0.72	< 0.0001
LAD	36.50 mm	59	62	0.69	< 0.0001

CP = *Optimum cut-off point;* S = *Sensitivity;* SP = *Specificity;* AUC = *Area under the curve;* p = *p-value;* FPD= *Filtered P-wave duration;* RMS *40, 30, 20 = root mean square voltage of the potentials in the last 40, 30, 20 ms of the filtered P-wave;* PL<*3 = Filtered P-wave late potential durations below 3 μV;* P *on* ECG = *Duration of the longest P-wave on the conventional electrocardiogram;* LAD = *Left atrium diameter on the echocardiogram.*

Table 3 - Cut-off points and performance estimates calculated by the ROC curve

the authors only found three patients (2.3%) with an abnormal P-SAECG.

Applying these criteria to our study – FPD ≥ 132 ms and RMS 20 ≤ 2.3 μV – the following performance estimates were obtained: sensitivity = 20.51%, specificity = 100%, positive predictive value = 100%, and negative predictive value = 40.76%.

Klein and associates[6] studied 45 patients before myocardial revascularization surgery, confirming that the sixteen patients that presented atrial fibrillation in the post operative period had an average FPD length of 163 ± 19 ms on the P-SAECG which was significantly higher than the group of 29 patients that did not present arrhythmia (p = 0.005). An enlarged left atrium on the conventional electrocardiogram demonstrated an insubstantial correlation (p = 0.04) for both groups. The variables, P-wave duration on the D2 lead, left ventricular hypertrophy, age, gender, hypertension and left ventricular ejection fraction were not significantly different between the groups. They concluded that the P-SAECG in patients before coronary artery surgery was an effective predictor of post operative atrial fibrillation. The correlations were similar to our study, however, the value found by those authors for FPD in the group with PAF was 163 ± 19 ms, while ours was 139.79 ± 16.63 ms.

The differences in the values found on the P-SAECG in the various studies[6-12] can be explained by differences in the arrhythmogenic substrates of the patients. Additionally, it should also be considered that different methods were used, particularly in relation to the trigger mode for signal recording and the filters used, which could contribute to difference in the final results.

Study limitations - Use of antiarrhythmic medication - In our study, 79.5% of the patients with PAF and 26.6% of those without PAF were using antiarrhythmic medication at the time of the P-SAECG. However, the results show that the use of antiarrhythmics did not significantly impact the analysis of the various parameters.

Manual measurements and adjustments - Occasionally, manual adjustments of the cursors were required to define the start and end of the amplified P-wave. In addition, all the measurements for late potential durations less than 3μV recorded on the P-SAECG were made manually. To lower the impact of this limitation, all adjustments and measurements were made by two observers and each detail was discussed until consensus was reached.

Conclusions

In comparison to the conventional ECG and echocardiogram, the time domain P-SAECG was a superior method for the proposed objective as seen in the performance estimates of the study.

The best parameters to distinguish patients with or without paroxysmal atrial fibrillation were the filtered P-wave duration and the P-wave late potential durations below 3 μV.

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