Time Domain Analysis of the Signal Averaged Electrocardiogram to Detect Late Potentials in Heart Failure Patients with Different Etiologies

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Objective

To evaluate the frequency, clinical correlations and prognosis influence of late potentials on the of heart failure patients with different etiologies using the signal averaged electrocardiogram.

Methods

A 42 month study of the signal averaged electrocardiograms of 288 heart failure patients with different etiologies was conducted. The group of patients included 215 males (74.65%) and 73 females (25.35%) between the ages of 16 and 70 (mean 51.5, standard deviation 11.24). The heart failure etiologies were: hypertensive heart disease (78 patients, 27.1%); idiopathic dilated cardiomyopathy (73 patients, 25.4%); ischemic cardiomyopathy (65 patients, 22.6%); Chagas disease (42 patients, 14.6%); alcoholic cardiomyopathy (9 patients, 3.1%); peripartum cardiomyopathy (6 patients, 2.1%); valvular heart disease (2 patients, 4.2%) and viral myocarditis (3 patients, 1.04%). The variables included the duration of the standard QRS complex, duration of the filtered QRS complex, duration of the signal below 40μV and the root mean square of the last 40ms which were analyzed in regard to age, gender, etiology and mortality as well as the findings of the 12-lead electrocardiogram at rest, echocardiogram and ambulatory electrocardiogram. The statistical analysis tests used were: the Fisher exact probability test, Student's t-test, Mann Whitney test, variance analysis, Log-Hank and the Kaplan-Meyer method.

Results

Late potentials were diagnosed in 90 patients (31.3%) and there was no association with the etiologies. The presence of this condition is associated with: a lower maximum oxygen uptake during the ergospirometry ($p=0.001$); sustained and non-sustained ventricular tachycardia during Holter monitoring ($p=0.001$), sudden death and mortality ($p<0.05$). Patients that did not present late potentials had a higher overlife rate.

Conclusion

The presence of late potentials was not associated with the etiologies and proved to be an indication of a worse prognosis.

Key words

Heart failure, signal averaged electrocardiogram, prognosis.

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Late potentials are high frequency, low amplitude, microvolt-size (μV) signals at the end of the QRS complex and the beginning of the ST segment that are related to fragmented and delayed electrical activity in the ventricles, enabling the genesis of sustained ventricular tachycardia through reentry mechanism. Late potentials can be identified using a signal averaged electrocardiogram (SAECG)[1]. The presence of late potentials was detected in patients with ventricular aneurysms[2,3], tachycardia, ventricular fibrillation[4], and arrhythmogenic right ventricular dysplasia[5], and is associated with a higher frequency of sudden cardiac death[6].

In heart failure patients, the presence of late potentials has been investigated in small case studies that do not include patients with Chagas disease[6-8].

It is admitted that 40% of the deaths in heart failure patients are sudden and caused by cardiac arrhythmias[9-12]. The SAECG is a noninvasive and relatively simple method which is a useful tool to identify patients with a higher risk of developing lethal cardiac arrhythmias. We formulated the hypothesis that the discovery of late potentials could contribute to identify heart failure patients with a higher risk of death.

We outlined the present study to evaluate the presence of late potentials in a cohort of heart failure patients with different etiologies, their clinical associations and their relation with mortality.

Methods

Patients - The study included a cohort of 288 outpatients, 215 males (74.7%) and 73 females (25.4%), between the ages of 16 and 70 (51.5 ± 11.2).

The clinical evaluation included the patient's medical history, a physical examination, chest x-ray, 12-lead electrocardiogram, ambulatory electrocardiogram, signal averaged electrocardiogram, echocardiogram and ergospirometry. The follow-up timeframe was between July 1998 and December 2001 and varied from 8 to 42 months (36.0 ± 4.5). Follow-up for each patient started on the day of the SAECG and ended on the date of the last clinical observation or death.

Two hundred and eighty-eight individuals were evaluated: 78 (27.1%) hypertensive heart disease patients; 73 (25.4%) idiopathic dilated cardiomyopathy patients; 65 (22.6%) ischemic cardiomyopathy patients; 42 (14.6%) Chagas disease patients; 12 (4.2%) valvular heart disease patients; 9 (3.1%) alcoholic cardiomyopathy patients; 6 (2.1%) peripartum cardiomyopathy patients and 3 (1.0%) viral myocarditis patients. In order to facilitate the statistical analysis the last four etiologies mentioned above were combined in a single group named *others* which included 30 individuals (10.3%).

The patients were divided in two groups: Group 1 without late potentials and Group 2 with late potentials. Patient death ended the follow-up.

Diagnostic criteria – The Framingham criteria[13] was used to diagnose heart failure and was established if the patient had at least two major criteria or one major and two minor criteria.

The diagnosis of the heart failure etiology was based on criteria previously published in medical literature for patients with symptomatic heart failure or left ventricular systolic dysfunction. (World Health Organization / International Society and Federation of Cardiology, 1980, Report of 1995 World Health Organization / International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies, 1996 and International Statistical Classification of Diseases and Related Health Problems, tenth revision – CID 10, 1993) An ischemic cardiomyopathy diagnosis was made based on patients with symptomatic heart failure and left ventricular dysfunction that had a history of myocardial infarction, percutaneous transluminal coronary angioplasty, myocardial revascularization, stable angina pectoris, an altered electrocardiogram, myocardial ischemia demonstrated by an altered exercise stress test, myocardial perfusion scintigraphy or a cineangiocardiography showing an obstruction greater than 75%.

Inclusion criteria – Patients between the ages of 16 and 70 with a diagnosis of symptomatic congestive heart failure caused by ventricular systolic dysfunction were included in the study.

Exclusion criteria – Patients with the following conditions were excluded from the study: aortic aneurysm, artificial pacemaker, atrial fibrillation or flutter, pregnant women, recent (less than 3 months) myocardial infarction or heart surgery, unstable angina pectoris, presence of myocardial ischemia during the exercise stress test, hypertrophic cardiomyopathy, recent systemic infection, chronic obstructive pulmonary disease or neoplasias. Patients using amiodarone were not excluded.

Signal averaged electrocardiogram (SAECG) – The signal averaged electrocardiogram was recorded using the Arrhythmia Research Technology Inc. 1200 EPX machine. The Frank orthogonal X, Y and Z electrographic lead arrangement and a broad bandwidth bidirectional filter (0.05 to 250Hz) with a frequency cut-off (lower value) of 40Hz were used. An acceptable noise level was considered as $< 0.3\mu$V with a gain of 2000/4000.

Late potential diagnosis – The presence of late potentials was detected based on the criteria of the American College of Cardiology: 1) duration of the end of the QRS complex $\geq$ 114ms; 2) duration of the signal below 40μV $\geq$ 38ms; 3) root mean square voltage of the last 40ms $\leq$ 20μV. In accordance with the findings of Moraes[14], only the root mean square voltage in the last 40ms $\leq$ 14μV was used for the patients with a bundle branch block.

Variables studied – The variables studied included: a) age; b) gender; c) heart failure etiology; d) inactive area found with the 12-lead electrocardiogram; e) bundle branch blocks detected with the 12-lead electrocardiogram;

f) diameters of the left ventricle during the diastole and systole from the echocardiogram; g) left ventricle ejection fraction from the echocardiogram; h) maximum oxygen uptake during the ergospirometry; i) sustained ventricular tachycardia detected on the ambulatory electrocardiogram; j) duration of the standard QRS complex; k) duration of the filtered QRS complex; l) duration of the signal below 40μV; and m) the root mean square voltage of the last 40ms, on the signal averaged electrocardiogram.

Statistical analysis – Comparisons of the data between the two groups (with and without late potentials) and within the groups were conducted with the following statistical tests: 1) chi-square test or Fisher exact probability test for comparisons between two categorical variables with two categories each; 2) Student's t-test for comparisons between the averages of the two groups for continuous variables; 3) Mann – Whitney test (non-parametric), for comparisons between the two groups (with and without late potentials) for numerical variables (number of occurrences); 4) ANOVA (variance analysis), for comparisons between more than two groups in the case of continuous variables; 5) log-rank test to compare the survival curve; 6) Kaplan-Meier method for death related variables. The operational variables used were: sensitivity, specificity, accuracy, positive predicative value and negative predictive value.

The significance level was $p<0.05$. The statistical analysis was conducted using the statistical program SPSS for Windows.

Ethical aspects - The protocol was approved by the Scientific and Ethics Commission of the Hospital das Clínicas of the University of São Paulo Medical School. The patients were briefed on the details of the study and were included in the protocol after signing the free and informed consent form.

Results

Late potentials detected by the signal averaged electrocardiogram - Out of the total number of 288 individuals included in the study, 90 (31.3%) were diagnosed with late potentials (Table 1).

The duration of the standard QRS complex varied from 80 to 242ms (124.9 ± 31.3); the duration of the filtered QRS complex varied from 76 to 254ms (131.7 ± 33.90); the duration of the signal below 40μV varied from 6 to 183ms (33.0 ± 20.57); and the root mean square voltage during the last 40ms varied from 4.20 to 267.30μV (44.0 ± 42.42).

Late potentials in relation to clinical variables – Patients with late potentials had an older mean age (54.5 ± 10 versus 50.1± 11.5); (p=0.004).

Patients with late potentials presented a higher incidence of sustained ventricular tachycardia (32/37 – 86.5% vs. 5/37 – 13.5%) during the ambulatory electrocardiogram (p=0.001). Late potential sensitivity to identify this arrhythmia was 86.5%; specificity 76.9%; accuracy 78.1%; positive predictive value 35.6% and negative predictive value 97.5%.

No association was found between the heart failure etiology and the presence of late potentials. However, the durations of the standard QRS complex and the filtered QRS complex revealed different mean value indexes for Chagas disease and dilated cardiomyopathy in relation to the other etiologies (Table 2).

No correlation was found between the presence of late potentials in relation to gender, heart failure etiology, the presence of electrically inactive areas during the electrocardiogram at rest, the presence of right or left bundle branch blocks or the size of the heart chambers on the echocardiogram.

Table 1 – Clinical and Demographic Characteristics

Variable	Total # Patients	With Late Potentials	Without Late Potentials
Cohort studied	288	90	198
Age (years)	51.5 ± 11.24	54.5 ± 10.00*	50.1 ± 11.55
Gender			
Male	215 (74.65%)	68 (75.56%)	147 (74.24%)
Female	73 (25.35%)	22 (24.44%)	51 (25.76%)
Max. Oxygen Intake (ml/Kg/min)	19.59 ± 8.53	16.99 ± 8.16	20.78 ± 8.45 *
Ejection Fraction (%)	36.42 ± 8.64	35.93 ± 9.49	36.64 ± 8.24
Etiology			
Hypertensive Cardiomyopathy	78 (27.08%)	18 (20.00%)	60 (30.30%)
Dilated	73 (25.35%)	26 (28.89%)	47 (23.74%)
Cardiomyopathy Ischemic Cardiomyopathy	65 (22.57%)	19 (21.11%)	46 (23.23%)
Chagas Disease	42 (14.58%)	19 (21.11%)	23 (11.62%)
Others	30 (10.42%)	8 (8.89%)	22 (11.11%)
Sudden Death	29 (20.4%)	26 (89.7%)*	3 (10.3%)
Survival (months)	118 ± 25.73	22.92 ± 16.02*	37.23 ± 17.03
SVT	37(100%)	32(86.49%)*	5 (13.51%)

** p<0.05; SVT- sustained ventricular tachycardia.*

Table 2 – Descriptive Measures of the SAECG Variables according to Etiology

Variable	N	Mean	SD	Comparison
Standard QRS Duration				
Chagas Disease	42	133.50	34.54	p = 0.012
Dilated Cardiomyopathy	73	132.25	36.36	
Hypertensive Cardiomyopathy	78	119.33	26.11	
Ischemic Cardiomyopathy	65	118.20	26.94	
Other Cardiomyopathies	30	124.53	30.22	
Filtered QRS Duration				
Chagas Disease	42	137.88	35.77	p = 0.048
Dilated Cardiomyopathy	73	139.25	38.27	
Hypertensive Cardiomyopathy	78	125.79	30.53	
Ischemic Cardiomyopathy	65	125.68	27.82	
Other Cardiomyopathies	30	133.20	36.85	
Duration of QRS below 40 μV				
Chagas Disease	42	36,83	17.31	p ns
Dilated Cardiomyopathy	73	36.59	25.62	
Hypertensive Cardiomyopathy	78	28.59	15.22	
Ischemic Cardiomyopathy	65	32.38	21.57	
Other Cardiomyopathies	30	31.73	19.53	
QRS voltage during the last 40ms				
Chagas Disease	42	38.09	51.00	p ns
Dilated Cardiomyopathy	73	35.17	27.59	
Hypertensive Cardiomyopathy	78	51.58	45.91	
Ischemic Cardiomyopathy	65	44.27	42.18	
Other Cardiomyopathies	29	53.66	47.21	

ns= not significant

From the 288 patients in the study, 142 (49.3%) died; 49 (17.0%) had late potentials and 93 (32.3%) did not have late potentials.

Cause of death was classified as: heart disease evolution, sudden death and other causes not related to heart failure (pneumonia, digestive hemorrhage, stroke, etc.) Eighty patients (56.3% of the total number of deaths) died as a result of heart failure evolution. From these 80 patients, 21 (26.3%) had late potentials and 59 (73.7%) did not. Twenty-nine patients suffered sudden death (10.1%) of which 26 had late potentials (89.5%) and 3 (10.3%) did not ($p<0.05$). Of the 29 patients that suffered sudden death, 17 (58.6%), had late potentials and had presented a previous episode of sustained ventricular tachycardia (Table 3).

The following observations were noted in relation to the evolution of the patients: a) adverse evolution (sustained ventricular tachycardia, sudden death or death as a result of heart failure evolution); and b) favorable evolution (none of the complications described). One hundred and seventy-seven patients (61.5%) had a favorable evolution of which 42 (46.7%) had late potentials and 135 (68.2%) did not. One hundred and eleven (38.5%) had an adverse evolution of which 48 (53.3%) had late potentials and 63 (31.8%) did not. (p=0.001) (Table 4).

The overlife rate was lower in the group with late potentials.

Late potentials in relation to echocardiograph findings – The diameter of the left ventricle during the diastole and systole, the diameter of the left atrium and the left ventricle ejection fraction were analyzed. The diameter of the left atrium varied from 27 to 80mm (mean 47.36; standard deviation 7.47). The diameter of the left ventricle during the diastole varied from 40 to 105mm (mean 73.98; standard deviation 9.57).

Table 3 – Presence of Late Potentials and Cause of Death

Cause of Death	Number of Patients	With Late Potentials	Without Late Potentials
Heart Failure	80 (56.4%)	21 (26.3%)	59 (73.7%)
Sudden Death	29 (20.4%)	26 (89.7%)	3 (10.3%)
Other Causes	33 (23.2%)	2 (6%)	31 (94.0%)
Total	142 (100%)	49 (34.5 %)	93 (65.5%)

Table 4 - Distribution of the Evolution in Regard to Late Potentials

	Late Potential						
	With		Without		Total		
Variable	n	%	n	%	n	%	Comparison
Evolution							
Favorable	42	46.67	135	68.18	177	61.46	p = 0.001
Adverse	48	53.33	63	31.82	111	38.54	Fisher Exact test
Total	90	100.00	198	100.00	288	100.00	

The diameter of the left ventricle during the systole varied from 30 to 95mm (mean 63.71; standard deviation 8.64). No significant differences were found in relation to late potentials for the echocardiogram variables studied.

Late potentials in relation to the ergospirometry – The analysis of maximum oxygen uptake varied from 4.6 to 33.7 ml/Kg/min (mean 19.59; standard deviation 8.53). In the patients that presented late potentials a value of 16.99 ml/Kg/min with a standard deviation of 8.16 was found. For the patients that did not have late potentials this value was significantly higher, that is, 20.78 ml/kg/min with a standard deviation of 8.45 (p=0.001).

Discussion

This study presented some significant observations. The most important finding was the confirmation that the presence of late potentials with congestive heart failure is related to an adverse prognosis with a higher incidence of sustained ventricular tachycardia and cardiac sudden death. More than one half of the patients (53.3%) with late potentials presented an unfavorable evolution and 26 of the 29 patients that suffered a sudden death had late potentials. The findings of this study are in agreement with those of Ohnishi et al[6]. These authors described a high incidence of ventricular arrhythmias and sudden death in 54 patients with dilated cardiomyopathy and an altered signal-averaged electrocardiogram using the following criteria for detecting late potentials: duration of the filtered QRS complex >120ms or the root mean square voltage in the last 40ms < 20μV. Nevertheless there is controversy. The studies of Meinertz et al[7] and Middlekauff et al[8] did not find the signal averaged electrocardiogram to be predictive of sudden death or ventricular arrhythmia. The number of patients in both of these studies was low (30 and 22 patients, respectively) and they used different criteria to detect late potentials. Only one of the 30 patients in the non-ischemic cardiomyopathy group of Meinhertz et al[7] had an altered signal averaged electrocardiogram. Eleven patients died during the course of the study of which 5 were a result of heart failure evolution. The author concluded that the signal averaged electrocardiogram was not predictive of sudden death even though the sample was too small to make any definite conclusions.

The finding that there is a higher incidence of male individuals 215 (74.7%) with heart failure is in agreement with reliable studies such as the Framingham study. Nevertheless, the direct relationship between aging and a higher incidence of late potentials found in this study was a new fact even though aging has already been identified as a contributing factor for a worse prognosis. This was demonstrated in the Framingham study and revealed that for each decade of life mortality rates increase by 27% for males and by 61% for females.

No association was found between heart failure etiologies and late potentials. It is possible that late potentials and arrhythmia are generated by a common mechanism that is involved in the various etiologies that lead to heart failure. Interstitial fibrosis and myocardial hypertrophy are frequently found in biopsies of patients with dilated cardiomyopathy, Chagas disease, ischemic cardiomyopathy, etc. which can cause abnormal electrical conduction. It has been demonstrated that the signal averaged electrocardiogram is a useful tool to identify patients with delayed ventricular activation and consequently a substrate to trigger arrhythmia. This study demonstrated a correlation between the standard QRS complex and the filtered QRS complex in relation to dilated cardiomyopathy and Chagas disease. It is known that these pathologies lead to a sporadic fibrotic process in the heart. A specific study to enable the noninvasive investigation of the extent of myocardial fibrosis and signal averaged electrocardiogram variables was proposed by Yamada et al[15]. The group studied 32 patients with dilated cardiomyopathy using a myocardial biopsy and a signal averaged electrocardiogram. They found a direct relationship between the extent of the fibrotic area and the duration of the filtered QRS complex (p<0.001), duration of the signal below 40μV (p<0.001) and the root mean square voltage in the last 40ms (p<0.005).

The presence of late potentials on the signal averaged electrocardiogram has demonstrated its predictive value for sudden death in heart failure patients[16-19]. The objective of the present study was investigate similar correlations for congestive heart failure caused not only by heart failure but also by other etiologies.

In relation to the findings on the echocardiogram, surprisingly, not even the ejection fraction or the left ventricle diameter during the diastole - variables identified

as main heart failure capacity quantifiers - demonstrated a correlation with alterations on the signal averaged electrocardiogram. However, the maximum oxygen uptake during the ergospirometry was correlated and therefore is a good variable to analyze the peripheral component of heart failure.

Individuals with His bundle blocks are usually excluded from time domain SAECG studies, since the ventricular activation alterations can either mask or simulate late potentials. In patients with bundle branch blocks, abnormal myocardial zones generating low amplitude signals could be completely masked by the delayed activation of the normal myocardial regions. However, false positive results can be obtained when the high frequency filters are placed over the end portion of a QRS complex that has a lower than normal amplitude.

There is disagreement regarding the exclusion of patients with bundle branch blocks from studies involving time domain signal averaged electrocardiograms. According to Moffa [20], the incidence of malignant ventricular arrhythmia in this group is higher than in individuals without conduction abnormalities (14% versus 4%). Additionally, the incidence of bundle branch blocks is relatively high in individuals with heart failure. (In this study there were 121 patients – 42.0%). Some authors have established different criteria to identify late potentials in patients with bundle branch blocks. For Nalos et al[21], late potentials are considered positive in the presence of a bundle branch block when all three variables analyzed in the time domain are abnormal, using the following reference values: filtered QRS complex $\geq$ 120 ms, duration of signal below 40μV $\geq$ 40ms and root mean square voltage in the last 40ms $\leq$ 15 μV. For Fontaine et al[22], the criteria that they considered as the best indicator was a root mean square voltage in the last 40ms of $\leq$17μV, with or without a signal below 40 μV for a duration $\geq$ 55ms. For these authors the additional requirement of a filtered QRS complex > 180ms does not alter the total predictive accuracy.

In this study, late potentials in the patients with bundle branch blocks were identified using the criteria of Moraes[14], a method used subsequently in other studies[23].

A standard QRS complex duration greater than or equal to 120ms presented a significant correlation with the prognosis (already proven in individuals with left bundle branch blocks) and 63 patients (70%) with this condition presented an adverse evolution.

The possible influence of medications is a point to be questioned. According to the experience of some authors[24,25], the interpretation of the signal averaged electrocardiogram results is jeopardized for the patients in group 1 using antiarrhythmic drugs and amiodarone. However, a prospective study[26] with 27 cases of dilated cardiomyopathy was conducted to analyze the use of amiodarone and its correlation with the signal averaged electrocardiogram. This study used a series of recordings from the signal averaged and conventional electrocardiograms that were taken before the administration of amiodarone, 2 months after the administration of amiodarone and subsequently with 3 month intervals. In comparison with the initial findings there was an increase in the duration of the filtered QRS complex however there was no alteration in the QRS voltage during the last 40ms. The incidence of late potentials remained constant. In this study, 21 (7.3%) of the individuals used amiodarone and the drug was not suspended as these patients had serious heart failure and a high risk of developing cardiac arrhythmia.

Conclusions

The etiology that led to heart failure has no correlation with the incidence of late potentials detected by the time domain signal averaged electrocardiogram. The presence of late potentials is related to a higher incidence of sustained ventricular tachycardia and cardiac sudden death. Expected overlife was lower in the individuals that presented late potentials. Therefore, the presence of late potentials on the signal averaged electrocardiogram proved to be an indication of an unfavorable prognosis in individuals with congestive heart failure.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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