Application of Signal Averaged Electrocardiography and Ejection Fraction for Prediction of Cardiovascular Arrhythmic Events

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Abstract: The objective of this study was to predict the future cardiovascular events including life threatening cardiac arrhythmias, in different cardiac diseases. An essential step in this process is the use of non-invasive techniques to screen patients and identify those at risk. The detection of ventricular late potential using the signal averaged electrocardiography (SAECG) as a non-invasive technique is being explored for this purpose. The study was conducted on 152 subjects selected from the OPD and admitted case of the New Civil Hospital and Government Medical College, Surat; between 30 to 80 years of age group, from August 2004 to October 2007. Eighty healthy subjects free from any major acute/chronic illness were selected as a control using our own normative values for SAECG. The statistical analysis was performed using SPSS package. The results obtained were analyzed for significance by using Chi square and Independent t test. When we compare the cardiac arrhythmic events on 6 month follow-up study based on SAECG and EF% separately we found that negative predictive value of SAECG was more (99.1%) than negative predictive value of EF% (93.6%). However positive predictive values for cardiac arrhythmic events of SAECG were less (28.9%) compare to EF% (42.9%). When both the parameters SAECG and EF% are considered together the negative as well as positive predictive values of these tests were quite high (100 and 50%, respectively). In this study, we found that SAECG and EF% together were an accurate predictor of the cardiac arrhythmic events in terms of positive and negative predictive value while SAECG or EF% alone were not. However SAECG has got a more negative predictive value compare to EF%. In this study SAECG compared favorably or even better than EF% for risk stratification. SAECG and EF% together (and not separately) may be considered as a better investigational tool to stratify future cardiovascular arrhythmic events.

Key words: Arrhythmic events, SAECG, EF%
INTRODUCTION

A signal-averaged electrocardiogram (SAECG) is a specialized ECG which may identify areas of delayed electrical conduction of the heart. Signal-averaged electrocardiogram (SAECG) reveals presence of late potentials that are low-amplitude high-frequency waveforms within the terminal portion of the QRS complex (Kathy and Chu-Pak, 2005). Delayed conduction, which usually occurs near cardiac scar tissue, is often associated with certain abnormal heart rhythms. Late potentials in the SAECG reflect the presence of slow conduction within the ventricular myocardium that may serve as a substrate for arrhythmogenesis. Late Potentials (LP) detected on the signal-averaged electrocardiogram (SAECG) predict arrhythmic events after acute myocardial infarction (Evrengul et al., 2004). Park et al. (2009) found that late potentials has a more positive predictive value than ejection fraction.

Fatal or near-fatal arrhythmias can be predicted by many risk stratification methods, especially by heart rate variability, in patients with reduced LVEF after AMI (Huikuri et al., 2009). Time domain signal averaging is applicable to a limited study group since, late potentials are not detectable in the presence of intraventricular conduction abnormalities such as bundle branch block with signal averaging very low amplitude electrical potential, generated by the sinus node, AV node, bundle of his and bundle branches are detectable at the body surface (Braunwald, 2006). Risk stratification of patients recovering from acute myocardial infarction is one of the most important functions for subsequent management and rehabilitation. Identifying patients at risk for serious ventricular arrhythmia is as important in this. Late potential at SAECG are said to suggest presence of electric instability and slowed conduction velocity, a pre-requisite for re-entrant ventricular tachyarrhythmia (Grimm et al., 2000). Progressive increase in delayed ventricular conduction by SAECG not associated with significant echocardiographic changes (Antonio et al., 2006). Therefore, the conduction disturbance seems to increase independently from anatomical alterations. The baseline SAECG and echocardiographic parameters, more than their modifications during follow-up, appear to be useful in identifying patients with sustained ventricular tachycardia (Antonio et al., 2006).

The 2006 American College of Cardiology, American Heart Association and European Society of Cardiology guidelines for management of patients with ventricular arrhythmias and prevention of sudden death list SAECG with a Class IIb recommendation (Class IIb noted as usefulness/efficacy is less well established by evidence/opinion). The report notes that SAECG may be useful to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or at risk for life-threatening ventricular arrhythmias (Zipes et al., 2006).

A recent consensus document from the American Heart Association, American College of Cardiology Foundation and Heart Rhythm Society indicates that SAECG may identify patients with prior MI at risk for sudden cardiac death and that further studies are required to assess the utility of this test (Goldberger et al., 2008).

One study from Japan (Ueno et al., 2007) did evaluate the use of SAECG in a study of 222 hospitalized patients found to have Non-Sustained Ventricular Tachycardia (NSVT). Forty-three patients had ischemic heart disease and 50 had non-ischemic cardiomyopathy. These patients were evaluated using an algorithm for risk-stratification. The algorithm included left ventricular ejection fraction, signal-averaged electrocardiography (in 69 patients), programmed ventricular stimulation and family history of Sudden Cardiac Death (SCD), programmed stimulation was done in follow-up to all positive SAECG studies.
The researchers concluded that this proposed algorithm for risk-stratification of patients with NSVT may be feasible for appropriate selection of candidates for prophylactic ICD implantation.

Sudden cardiac death remains an important public health problem. The availability of effective treatment in terms of the implantable defibrillator makes it critical to be able to identify individuals at risk. An essential step in this process is the development of non-invasive techniques to screen patients who may be at risk. The detection of ventricular late potential using the SAECG has been a non-invasive technique for this purpose. Although it has a low positive predictive value, SAECG has also been shown to predict susceptibility to ventricular arrhythmias (Grimm et al., 2000, 2003). The aim of the study was to predict and stratify the future cardiovascular events including life threatening cardiac arrhythmias in different cardiac diseases through positive and negative predictive values of SAECG and EF %.

MATERIALS AND METHODS

All the patients/guardians were informed about the study protocol and informed written consent was obtained from them to participate in the study prior to examination and investigation. The study was approved by the Ethical Committee of Government Medical College and New Civil Hospital, Surat and written informed consent was obtained from all the participants. Two hundred and twenty-seven subjects were selected from the OPD and admitted case of the New Civil Hospital and Government Medical College, Surat between 30 to 80 years of age group, from August 2004 to October 2007. Out of the 227 only 152 patients were included in the study group based on the inclusion and exclusion criteria. Eight healthy subjects free from any major acute/chronic illness were selected as a control. The patients were divided into the following groups:

- Acute Coronary Syndrome (ACS) from the last 6 to 10 weeks - 58 patients
- Chronic Ischemic Heart Disease (CIHD) - 46 patients
- Systemic Arterial Hypertension (SAH) - 27 patients
- Dilated Cardiomyopathy (DCM) - 21 patients

SAECG was taken using HIPEC HA-200 system analyzer with Butterworth filter of 40-250 Hz. Thirty six leads were used to obtain three different leads (X, Y and Z) and a mini computer averaged them into one single complex for analysis. The computer selected a part of the down slope of the R wave that first dropped to an arbitrary point (usually 40 µV), this signaled the beginning of late potential. Three measurements were then made.

- QRS duration (QRSd) which includes late potential
- Duration of Late Potential (LP)
- Root mean square voltage of the terminal 40 ms sec of the QRS complex (RMS40)

Out of the three parameters of SAECG at least two parameters should be abnormal to diagnose SAECG as abnormal.

Defining the Normative Values of Different Parameters of SAECG

We have established our own normative values of SAECG. Eight subjects free from any cardiac illness or any major acute/chronic illness, were selected for SAECG to established normative values.
The parameters of SAECG and their normal values are:

- QRS Duration = 110 m sec
- RMS_{s0} > 25 μV
- Late Potential (LP) duration < 40 m sec

The 5th and 95th percentile of each parameter was decided.

**QRS Duration**
Upper limit is important so 95th percentile was considered as cut of point

**RMS_{s0}**
Lower limit is important so 5th percentile was considered as cut of point.

**Late Potential (LP) Duration**
Upper limit is important so 95th percentile was considered as cut of point.

These values are matching with the normal values decided by American Heart Association (AHA) and also by other investigators (Braunwald, 2006). The SAECG is said to be positive only if at least 2 parameters of SAECG are abnormal. Two D Echocardiography was performed in all the study population to support the diagnosis and also on the control group aged 35 years to rule out asymptomatic cardiac illness.

Preparation of the patients before electrode placement is very important for SAECG analysis. Shave the chest and the areas where the leads are to be placed followed by rubbing of the skin by gauze pad. Clean the area with alcohol pad and then dry the skin. Place the electrode on the flat bony areas and not on muscle or fat. Connect the patient with SAECG analyzer.

Follow up visits were done for at least 6 months at an interval of 15 days for the symptomatic patients while an interval of one month for asymptomatic cases. For all patients an arrhythmia event was considered only if a patient had a documented arrhythmia in the hospital. The statistical analysis was performed using SPSS package. The results obtained were analyzed for significance by using Chi square and t-test.

**RESULTS**

The study group comprised cases (n = 152) includes acute coronary syndrome from the last 6-10 weeks (n = 58), chronic ischemic heart disease (n = 46), systemic arterial hypertension (n = 27), dilated cardiomyopathy (n = 21) (Table 1). The number of cases with SAECG positivity was quite high in patients with ACS (50%) than other groups (CIHD DCM 23.7%, DCM18.4% and SAH 7.9%, Table 2). This result is similar to the study by previous investigators (Braunwald, 2006; Savard et al., 1997). Table 3 shows that out of the total

<table>
<thead>
<tr>
<th>Group status</th>
<th>Age (years)</th>
<th>RMS_{s0} (μV)</th>
<th>QRSd (m sec)</th>
<th>LP (m sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases n = 152</td>
<td>55.8±9.8</td>
<td>49.8±38.8</td>
<td>99.7±20.3</td>
<td>31.6±20.5</td>
</tr>
<tr>
<td>Control n = 80</td>
<td>50.5±9.1</td>
<td>87.5±40.6</td>
<td>91.1±12.4</td>
<td>23.9±7.7</td>
</tr>
</tbody>
</table>

P Value

Values are expressed as Mean±SD. Cases (n=152) includes Acute Coronary Syndrome (ACS) from the last 6-10 weeks-58 patients, Chronic Ischemic Heart Disease (CIHD)-46 patients, Systemic Arterial Hypertension (SAH)-27 Patients, Dilated cardiomyopathy (DCM)-21 Patients. RMS_{s0}: Root mean square voltage of terminal 40 second of QRSd, QRSd: QRS duration, LP: Late potential.
Table 2: SAECG abnormality in different cardiovascular disease

<table>
<thead>
<tr>
<th>Study groups</th>
<th>SAECG positive</th>
<th>SAECG negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS (n = 58)</td>
<td>19 (58)</td>
<td>39</td>
</tr>
<tr>
<td>CIHD (n = 46)</td>
<td>9 (23.7)</td>
<td>37</td>
</tr>
<tr>
<td>SAH (n = 27)</td>
<td>3 (7.9)</td>
<td>24</td>
</tr>
<tr>
<td>DCM (n = 21)</td>
<td>7 (18.4)</td>
<td>14</td>
</tr>
<tr>
<td>Total (n = 152)</td>
<td>38</td>
<td>114</td>
</tr>
</tbody>
</table>

Values in parenthesis indicates % of the number of total SAECG positive, ACS: Acute coronary syndrome, CIHD: Chronic ischemic heart disease, SAH: Systemic arterial hypertension, DCM: Dilated cardiomyopathy

Table 3: Correlation of SAECG positivity to abnormal cardiac arrhythmic events (arrhythmias) on 6 months follow-up in various cardiac diseases

<table>
<thead>
<tr>
<th>Group status</th>
<th>SAECG status</th>
<th>Cardiac events positive on 6 month follow-up</th>
<th>Cardiac events negative on 6 month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS (n = 58)</td>
<td>Positive (n = 19)</td>
<td>07 (36.8)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Negative (n = 39)</td>
<td>00 (100)</td>
<td>39</td>
</tr>
<tr>
<td>CIHD (n = 46)</td>
<td>Positive (n = 09)</td>
<td>01 (11.1)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Negative (n = 37)</td>
<td>00 (100)</td>
<td>37</td>
</tr>
<tr>
<td>SAH (n = 27)</td>
<td>Positive (n = 03)</td>
<td>01 (25)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Negative (n = 24)</td>
<td>00 (100)</td>
<td>24</td>
</tr>
<tr>
<td>DCM (n = 21)</td>
<td>Positive (n = 07)</td>
<td>02 (28.6)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Negative (n = 14)</td>
<td>01 (92.9)</td>
<td>13</td>
</tr>
<tr>
<td>Total (n = 152)</td>
<td>Positive (n = 38)</td>
<td>11 (28.9)</td>
<td>27*</td>
</tr>
<tr>
<td></td>
<td>Negative (n = 114)</td>
<td>01 (99.1)</td>
<td>113 **</td>
</tr>
</tbody>
</table>

Table 3 shows that out of the total 38 SAECG positive patients, 11 patients demonstrate abnormal cardiac events (cardiac arrhythmia) on 6 months follow-up (positive predictive value 28.9%); while out of the total 114 SAECG negative patients only one patient presented with cardiac arrhythmia on 6 months follow-up (negative predictive value 99.1%). This indicates that SAECG has more negative predictive value than positive predictive value. Values in parenthesis indicate percentage of positive and negative predictive value: *p<0.005, **p<0.0005, Cardiac arrhythmic events = Ventricular tachycardia/ventricular fibrillation/sudden cardiac death, ACS: Acute coronary syndrome, CIHD: Chronic ischemic heart disease, SAH: Systemic arterial hypertension, DCM: Dilated cardiomyopathy

Table 4: Correlation between abnormality of EF% and cardiac arrhythmic events in the study population

<table>
<thead>
<tr>
<th>Study group based on EF%</th>
<th>Cardiac arrhythmic events</th>
<th>No cardiac arrhythmic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF&lt;40% (n = 42)</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>EF=40% (n = 110)</td>
<td>3</td>
<td>107</td>
</tr>
</tbody>
</table>

Positive predictive value = 23.8%, Negative predictive value = 97.3% Cardiac arrhythmic events = Ventricular tachycardia/ventricular fibrillation/sudden cardiac death, EF%: Percentage ejection fraction

Table 5: Cardiac arrhythmic events on 6 months follow-up in the study population based on EF%

<table>
<thead>
<tr>
<th>Study group based on EF%</th>
<th>Cardiac events on 6 months follow-up</th>
<th>No cardiac events on 6 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF&lt;40% (n = 42)</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>EF=40% (n = 110)</td>
<td>7</td>
<td>103</td>
</tr>
</tbody>
</table>

Positive predictive value = 42.9%, Negative predictive Value = 93.6% Cardiac arrhythmic events = Ventricular tachycardia/ventricular fibrillation/sudden cardiac death, EF%: Percentage ejection fraction

38 patients with SAECG positive (i.e., 2 parameters of SAECG are abnormal), 11 patients demonstrate abnormal cardiac events (Cardiac Arrhythmia) on 6 month follow-up (positive predictive Value 28.9%); while out of the total 114 SAECG negative patients only one patient presented with cardiac arrhythmia on 6 month follow-up (negative predictive value 99.1%). Thus, indicating that SAECG has more negative predictive value than positive predictive value in stratifying the risk for the future cardiac arrhythmic events in any patients with cardiac diseases. Study by various authors also corroborate with our results i.e., negative predictive value of SAECG was more than positive predictive value for any cardiac arrhythmic events (Savard et al., 1997). Table 3-6 summarizes the incidence of cardiac arrhythmic events based on SAECG and EF% when taken separately and together. When we compared the cardiac arrhythmic events on 6 months follow-up study based on SAECG and EF% separately we found that negative predictive value of SAECG was more
Table 6: Cardiac arrhythmic events in acute coronary syndrome based on EF% and SAECG taken together in the study population

<table>
<thead>
<tr>
<th>Study group based on EF % and SAECG</th>
<th>Cardiac events</th>
<th>No cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAECG-ve and EF=40% (n = 68)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>SAECG-ve and EF&lt;40% (n =12)</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>SAECG-ve and EF =40% (n = 07)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>SAECG-ve and EF =40%(n = 31)</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Total (n =58)</td>
<td>5</td>
<td>53</td>
</tr>
</tbody>
</table>

Positive predictive value = 99.1%, Negative predictive value = 100% Cardiac arrhythmic events = Ventricular tachycardia/ventricular fibrillation/sudden cardiac death, EF%: Percentage ejection fraction, SAECG: Signal averaged ECG

(99.1%, Table 3) than negative predictive value of EF% (93.6%, Table 5). However, positive predictive values for cardiac arrhythmic events of SAECG were less (28.9%, Table 3) compared to EF% (42.9%, Table 5). When both the parameters i.e., SAECG and EF% were considered together, the negative as well as positive predictive values of these tests were quite high (100 and 50%, respectively). This has been in conformity with the observation of previous study (Turitto et al., 1988a).

DISCUSSION

In recognizing potentially useful markers, late potentials spotted on SAECG appeared to be the most useful tool for identifying prospective patients at risk for future ventricular arrhythmic events and sudden cardiac death.

We compared SAECG with EF%, as both have the advantage of being non-invasive methods of assessment also both have positive as well as negative predictive value of the future ventricular arrhythmic events. This study conducted on 152 patients. We found that SAECG and EF% together were accurate predictors of the cardiac arrhythmic events in terms of positive and negative predictive value (Table 6) and not SAECG or EF% alone (Table 3-5). However, SAECG has got a more negative predictive value compare to EF% (Table 3). Present study is well supported by Bailey et al. (2001) of the utility of non-invasive tests for risk stratification and prediction of cardiovascular arrhythmic events was found to be helpful. The researchers concluded that combinations of tests in stages allowed the researchers to stratify 92% of patients as either high-risk or low-risk. A report from the 2006 American College of Cardiology, American Heart Association and European Society of Cardiology guidelines for management of patients with ventricular arrhythmias and prevention of sudden death list SAECG with a Class IIb recommendation (Class IIb noted as usefulness/efficacy is less well established by evidence/opinion). However the report noted that SAECG may be useful to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or at risk for life-threatening ventricular arrhythmias (Zipes et al., 2006).

In a study of (n = 2461, Savard et al., 1997) post myocardial infarction patients it was found that SAECG was a statistically significant predictor of arrhythmic events during 1-2 year follow up with a sensitivity of 65% and a specificity of 68.4%. Various previous studies (Turitto et al., 1988a; El-Sherif et al., 1989) with non-sustained ventricular tachycardia states that SAECG was a predictor of ventricular tachycardia, with specificity in the range of 71 to 89%, comparing well with the values of specificity (92 to 99%) for SAECG alone in present study. In some of the larger studies, SAECG achieved statistical significance with moderate values of sensitivity and very high specificity (Turitto et al., 1988b).

One study from Japan (Ueno et al., 2007) did evaluate the use of SAECG for stratification and prediction of arrhythmic events for selection of candidates for prophylactic ICD implantation and they found it feasible. Goldberger et al. (2008) observed that SAECG may identify patients with prior MI at risk for sudden cardiac death and that further studies are required to assess the utility of this test.
Thus, the significance of positive as well as negative predictive value of SAECG to stratify the risk of future cardiovascular arrhythmic event is similar to the values obtained in other studies. But several other studies have confirmed that abnormal SAECG was not a strong predictor of sudden cardiac death. Bauer et al. (2005) reported on reduced prognostic power of ventricular late potentials in patients who received revascularization therapy. The researchers retrospectively analyzed the predictive values of late potentials, left ventricular ejection fraction and heart rate turbulence in a cohort of patients who survived a recent myocardial infarction from January 1996 to December 2000. The majority of these patients received contemporary post-myocardial infarction treatment, namely, revascularization, beta-blockers, aspirin, ACE inhibitors and statins. The researchers found that the incidence of late potentials were low (9.3%) and that the presence of late potentials was not predictive of cardiac death and serious arrhythmic events. However, in their study left ventricular function was mostly preserved but depressed in our study. There was no significant correlation between parameters of the SAECG and two-dimensional ECG for the entire patient population.

CONCLUSION

Amongst the three components of SAECG namely QRS duration, RMS$_90$ and Late Potential (LP) duration prevalence of late potentials is high in cardiovascular disease like acute coronary syndrome, dilated cardiomyopathy, chronic ischemic heart disease and systemic arterial hypertension. The SAECG has very high negative predictive value for risk stratification of future cardiac arrhythmic events. The SAECG and EF% together (and not separately) may be considered as a better investigational tool to stratify future cardiovascular arrhythmic events.

In summary SAECG appears to be a useful new technique for identifying individuals at risk for cardiac arrhythmic events. In this study, SAECG compared favorably or even better than EF% for risk stratification. It looks ostensibly remarkable to consider these two measures (SAECG and EF%) because SAECG measures electrophysiological properties while EF% is a measure of contractile properties or mechanical properties of the heart. Thus, we can expect that these two measures would provide independent information on the risk of ventricular arrhythmias.

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REFERENCES


