Prognostic Value of an Abnormal Signal-Averaged Electrocardiogram in Patients With Nonischemic Congestive Cardiomyopathy

Donna M. Mancini, MD; Kar Lai Wong, MD; and Michael B. Simson, MD

Background. An abnormal signal-averaged ECG (SAECG) has predictive value for arrhythmic events in patients with coronary artery disease. The purpose of this study was to investigate whether an abnormal SAECG could provide prognostic information in patients with nonischemic dilated cardiomyopathy.

Methods and Results. We prospectively obtained SAECGs in 114 patients with dilated nonischemic cardiomyopathy. Twelve-lead ECGs, left ventricular ejection fractions, hemodynamic measurements, and peak exercise oxygen consumption (VO₂) also were measured. An SAECG was defined as abnormal by any one of the following criteria: filtered QRS duration >120 msec, root-mean-square voltage in the last 40 msec <20 μV, or duration <40 μV >38 msec at 40 Hz. Sixty-six patients had a normal SAECG, 20 patients had an abnormal SAECG, and 28 patients had bundle branch block (BBB). Mean follow-up was 10±5 months. Age, ejection fraction, peak VO₂, pulmonary capillary wedge pressure, and cardiac index were not statistically different among the three groups. Use of antiarrhythmic drugs was similar among the three groups, although patients with BBB had more implantable defibrillators (p<0.05). The incidence of previous atrial arrhythmias was similar for the three groups. Patients with abnormal SAECG or BBB had more past episodes of sustained ventricular tachycardia and/or sudden death episodes (n=9) than patients with normal SAECG (n=1) (p<0.01). Prospectively, none of the 66 patients with normal SAECG died suddenly or had sustained ventricular arrhythmias. Two deaths occurred from progressive heart failure, and three patients required urgent transplant. In the 20 patients with an abnormal SAECG, four patients had sustained ventricular tachycardia, five patients died suddenly, two patients died from progressive heart failure, and one patient required urgent transplant. In the patients with BBB, four patients had sustained ventricular tachycardia, and four patients required urgent transplant. One-year event-free survival, i.e., absence of ventricular tachycardia and/or death, was 95% in patients with normal SAECG, 88% in patients with BBB, and only 39% in patients with an abnormal SAECG (p<0.001). Multivariate analysis demonstrated that SAECG and New York Heart Association classification were independent predictors of survival.

Conclusions. Patients with an abnormal SAECG had a statistically significant increase in sustained ventricular arrhythmias and/or death than did patients with a normal SAECG or BBB. This study demonstrates that an abnormal SAECG is a marker of past and future arrhythmic events in patients with nonischemic dilated cardiomyopathy. In contrast, patients with a dilated cardiomyopathy with a normal SAECG have an excellent prognosis with adverse outcome only from progressive heart failure. (Circulation 1993;87:1083–1092)

KEY WORDS • electrocardiogram, signal-averaged • sudden death • dilated cardiomyopathy

Despite significant advances in the therapy of heart failure, the mortality for this disease remains high and increases with the severity of the disease. Approximately 40% of the deaths in patients with end-stage heart failure are sudden.1,2 Patients with chronic heart failure are at the greatest risk for sudden death than any other definable subset of patients in cardiovascular medicine.2 Although the survival of patients with nonischemic dilated cardiomyopathy is slightly better than that of patients with coronary artery disease, the incidence of sudden death is comparable.3,4 Our ability to identify patients at the greatest risk for sudden death is poor. Hemodynamic measurements cannot predict death from heart failure or arrhythmia.5 Nonsustained ventricular tachycardia (VT) on ambulatory monitoring is detected in up to 70% of patients with New York Heart Association (NYHA) class III or IV congestive heart failure; however, these complex ventricular arrhythmias predict total cardiac mortality, not specifically sudden death.6,7 Electrophysiologic testing in patients with dilated cardiomyopathy who have no prior symptomatic arrhythmias similarly does not reliably predict sudden death with a 30% risk of sudden death in the large segment of patients who are noninducible.6–8

Signal-averaged ECG (SAECG) allows the detection of late potentials, which have been associated with
TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Normal SAECG</th>
<th>Abnormal SAECG</th>
<th>Bundle branch block</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>114</td>
<td>66</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48±15</td>
<td>48±17</td>
<td>49±13</td>
<td>48±11</td>
</tr>
<tr>
<td>Sex (No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72 (63)</td>
<td>40 (61)</td>
<td>15 (75)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (37)</td>
<td>26 (39)</td>
<td>5 (25)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>NYHA class (mean±SD)</td>
<td>2.6±0.8</td>
<td>2.6±0.9</td>
<td>2.8±0.6</td>
<td>2.7±0.7</td>
</tr>
<tr>
<td>I (No.)</td>
<td>10 (9)</td>
<td>9 (14)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>II (No.)</td>
<td>35 (31)</td>
<td>19 (29)</td>
<td>7 (35)</td>
<td>9 (32)</td>
</tr>
<tr>
<td>III (No.)</td>
<td>56 (49)</td>
<td>30 (45)</td>
<td>11 (55)</td>
<td>15 (53)</td>
</tr>
<tr>
<td>IV (No.)</td>
<td>13 (11)</td>
<td>8 (12)</td>
<td>2 (10)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>14.8±5.5</td>
<td>15.0±5.6</td>
<td>14.5±6.7</td>
<td>14.4±4.3</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>22±9</td>
<td>22±9</td>
<td>21±9</td>
<td>22±11</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>19±10</td>
<td>19±10</td>
<td>18±8</td>
<td>20±10</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.1±0.5</td>
<td>2.2±0.6</td>
<td>2.0±0.5</td>
<td>2.2±0.5</td>
</tr>
<tr>
<td>Duration of follow-up (months)</td>
<td>10±5</td>
<td>10±6</td>
<td>10±5</td>
<td>10±5</td>
</tr>
<tr>
<td>Etiology (No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>57 (50)</td>
<td>27 (41)</td>
<td>12 (60)</td>
<td>18 (64)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (14)</td>
<td>14 (21)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>19 (17)</td>
<td>11 (17)</td>
<td>5 (25)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>5 (4)</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Valvular</td>
<td>7 (6)</td>
<td>5 (8)</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (6)</td>
<td>4 (6)</td>
<td>1 (5)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

SAECG, signal-averaged ECG; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; CI, cardiac index.

Values in parentheses indicate percentages.

delayed and disorganized ventricular activation. These recordings are similar to that observed on direct epicardial and endocardial electrograms recorded from patients with VT.9-14 Several prospective studies have demonstrated that an abnormal SAECG has predictive value for future ventricular events in patients with coronary artery disease.15-19 An increased incidence of abnormality on the SAECG in patients with nonischemic dilated cardiomyopathy who present with ventricular arrhythmias has also been demonstrated.20-23 Whether an abnormal SAECG can provide predictive information in patients with nonischemic cardiomyopathy remains unclear. The present prospective study was undertaken to determine the prognostic value of SAECG in patients with nonischemic dilated cardiomyopathy.

Methods

All patients with a dilated cardiomyopathy (n=114) who underwent heart failure or transplant evaluation at the Hospital of the University of Pennsylvania between September 1990 and March 1992 were included in the study. This evaluation included detailed history and physical examination, exercise testing with measurement of oxygen consumption, radionuclide left ventricular ejection fraction, and, in the majority of patients, right and left cardiac catheterization.

The diagnosis of nonischemic cardiomyopathy was confirmed by cardiac catheterization in 99 patients, autopsy in one patient, and negative exercise thallium test without historical or ECG evidence of myocardial infarct in the remaining 14 patients. The average age of the 72 men and 42 women was 48±15 years (range, 18-81 years). Etiology of heart failure was idiopathic in 50%, hypertension in 14%, and alcohol in 17%. Valvular heart disease, postpartum cardiomyopathy, myocarditis, and adriamycin cardiotoxicity accounted for the remaining 19%. The average NYHA classification was 2.6±0.8, with 9% of patients in class I, 31% in class II, 49% in class III, and 11% in class IV congestive heart failure (Table 1).

Ejection fraction was obtained from radionuclide angiography, cardiac catheterization, or both during the initial evaluation. Hemodynamic data were derived from Swan-Ganz catheterization performed with patients on their chronic medical regimen. Cardiac outputs were measured by thermodilution. Maximal treadmill exercise testing with respiratory gases was performed in all ambulatory patients using the modified Naughton protocol. Measurements of mixed expired oxygen, mixed expired carbon dioxide, and expired volume were determined at rest and every 30 seconds throughout exercise using a metabolic cart (SensorMedics, Anaheim, Calif.).

SAECG

SAECG was recorded using a commercially available system (Arrhythmia Research Technology, model 1200 EPX). Bipolar X, Y, and Z leads were used to record approximately 250 ECG cycles. Each signal-averaged lead was filtered with the use of a bidirectional filter at

See p 1405
patients managed primarily outside the clinic system was determined by telephone interview of referring physicians, patients, or both.

End points of the study were death and sustained ventricular arrhythmias. Deaths occurring out of hospital within 24 hours and without symptomatic deterioration were classified as "sudden." The deaths of patients with progressive symptomatic and/or hemodynamic deterioration were classified as resulting from progressive heart failure. Sustained VT was defined as symptomatic VT at a rate of >120 beats per minute for at least 30 seconds. Analysis was also performed using urgent transplant as an additional study end point. Urgent transplant was defined as cardiac transplantation performed with the patient hospitalized on parenteral inotropic and/or mechanical support.

**Statistical Analysis**

Differences in characteristics among patient groups were compared by ANOVA or $\chi^2$ analysis. Differences in characteristics within a patient group were compared by the nonpaired $t$ test. Probability of survival from the time of SAECG was analyzed by the life-table method. Survival curves were compared using the log-rank test and Wilcoxon analysis. Cardiac transplantation was considered a censored observation (i.e., withdrawn from study at the time of transplant).

The association of individual variables with survival was obtained by univariate analysis (Wilcoxon and log rank). Examined variables were normal or abnormal SAECG, bundle branch block present or absent, standard QRS duration above or below 120 msec, antiarrhythmic drug use present or absent, past history of VT, age, functional class, sex, pulmonary capillary wedge pressure, cardiac index, and peak VO$_2$. Multivariate analysis was also performed using the Cox proportional hazards model. The relation among variables was examined by linear regression analysis. A value of $p<0.05$ was considered significant. All data are expressed as mean±SD.

**Results**

**Clinical Characteristics**

The clinical characteristics of the 114 patients are outlined in Table 1 and Figure 1. Drug therapy and ECG characteristics are listed in Table 2. No statistically significant differences among the three groups were observed in regard to peak VO$_2$, ejection fraction, pulmonary capillary wedge pressure, cardiac index, NYHA classification, age, sex, etiology of heart failure, or duration of follow-up (Figure 1). Antiarrhythmic drug use was comparable between the three groups, although patients with bundle branch block had more implantable defibrillators ($p<0.05$) (Figure 2).

Ninety-five patients were in normal sinus rhythm, 14 patients were in atrial fibrillation, five patients were 100% ventricularly paced, and 39 patients met criteria for left ventricular hypertrophy. Eighteen patients had left bundle branch block, and five patients had right bundle branch block. The incidence of past atrial arrhythmias was similar among patients with normal SAECG, abnormal SAECG, and/or bundle branch block. Patients with an abnormal SAECG or bundle branch block had more past episodes of VT and/or
sudden death than did patients with a normal SAECG ($p<0.01$) (Figure 3).

**SAECG**

Standard QRS duration, filtered QRS duration, and duration of root-mean-square 40 were greater in patients with an abnormal SAECG than in patients with a normal SAECG, whereas the root-mean-square of last 40 msec was reduced (Table 3).

Of the 20 patients who had abnormal SAECG, 80% had filtered QRS duration $>120$ msec, 55% had root-mean-square 40 $<20$ $\mu$V, and 45% had duration $<40$ $\mu$V of $>38$ msec. Nine of the patients had an abnormal SAECG by more than one criteria. Of the 66 patients with a normal SAECG, only eight patients had a filtered QRS duration that ranged from 115 to 120 msec. Representative examples of a normal and abnormal SAECG are shown in Figure 4.

**Clinical Outcome**

Clinical outcome is summarized in Table 4. All deaths in the normal SAECG group were from heart failure. No patient in the group developed any significant arrhythmias prospectively. Three patients required urgent transplant.

In the patients with an abnormal SAECG, seven patients died. Five deaths were sudden, and two deaths resulted from progressive heart failure. Of the five sudden deaths, three patients died while asleep, and
two had witnessed arrests. None of the patients with sudden death had a past history of sustained ventricular arrhythmias. Four patients prospectively had VT, with only one of these patients having a prior history of VT. One patient who prospectively had VT also required urgent transplant.

In patients with bundle branch block, four patients prospectively had VT. These arrhythmias occurred in patients who had implanted defibrillators, and none died. Four patients required urgent transplant, one of which had VT prospectively.

The prospective adverse events were not clustered in any one etiologic subgroup. Adverse events occurred in 11 patients with idiopathic dilated cardiomyopathy, four patients with alcoholic cardiomyopathy, one patient with myocarditis, two patients with valvular disease, one patient with an endocrine-related cardiomyopathy, one patient with hypertrophic cardiomyopathy, and one patient with postpartum cardiomyopathy.

Thirteen of the 20 patients with an abnormal SAECG had either a past or prospective episode of sustained VT (n=6) or died (n=7). Only three of these patients did not have filtered QRS duration >120 msec. Seven patients met criteria by filtered QRS duration alone, with six patients exhibiting late potentials. Of the seven patients with an abnormal SAECG who did not have any adverse events, five of the seven patients had late potentials, and five had filtered QRS duration >120 msec. There were no statistical differences in filtered QRS duration, root-mean-square 40 <20 μV, and duration <40 μV in those patients with an abnormal SAECG who did well and those who had past or prospective adverse events (Table 5).

Of the 14 patients receiving antiarrhythmic agents, two developed VT, two died from progressive heart failure, and one required urgent transplant. Only four of the 11 patients with an abnormal SAECG who had a prospective event were receiving antiarrhythmic drugs. Only one of the three patients who had an abnormal SAECG and a past history of VT prospectively had a recurrent episode.

Clinical characteristics of patients with adverse events are summarized in Table 6. Adverse events were defined as VT, death, or urgent transplant. In this group, NYHA classification was significantly greater, and peak VO₂ and ejection fraction were significantly reduced compared with patients who had a good outcome (p<0.05 in all). No statistically significant difference was noted between the two groups in regard to resting hemodynamic measurements, although cardiac index tended to be higher in patients with a good outcome (p<0.08).

**Survival**

Cumulative survival for the entire 114 patients was 87% at 1 year. Patients with a normal SAECG had a 95% 1-year survival. This was similar to the 100% survival for patients with bundle branch block. One-year survival in patients with an abnormal SAECG was significantly decreased at 56% (p<0.0001 versus both groups) (Figure 5).

Event-free survival with events defined as VT or death for the entire group was 81% at 1 year. The percent of patients at 1 year without significant events was 95% for patients with normal SAECG, 88% for patients with a bundle branch block, and 39% for patients with abnormal SAECG (p<0.0001 versus both groups) (Figure 6).

Analysis performed using urgent transplant defined as a death rather than a censored observation yielded a 1-year survival of 80%. With division of patients into the three groups, 1-year survival was 90%, 56%, and 82% for normal SAECG, abnormal SAECG, and bundle branch block groups, respectively (p<0.04). One-year event-free survival with events defined as VT, death, or urgent transplant for the entire group was 75%. With division of patients into three groups, 1-year event-free rates were 90%, 39%, and 75% (p<0.0005) for patients with normal SAECG, abnormal SAECG, or bundle branch block, respectively. With analysis performed using urgent transplant as an additional end point, the worst prognosis was consistently in patients with an abnormal SAECG, although this was not significantly different from patients with bundle branch block. Deletion of patients receiving type IA or III antiarrhythmic drugs did not alter the 1-year event-free rate, which remained 91%, 39%, and 74% for the normal SAECG, abnormal SAECG, and bundle branch block groups, respectively. When patients with past VT were excluded, the prospective 1-year event-free rate was 89%, 25%, and 89% for the respective groups.

**Univariate and Multivariate Analyses**

Univariate and multivariate analyses were performed using death, urgent transplant, and VT as end points to increase the number of adverse outcomes. An abnormal SAECG and the NYHA classification predicted an adverse outcome by both univariate and multivariate analyses. With all of the confounders, including NYHA class controlled, the relative risk estimate (actually an odds ratio) for abnormal versus normal SAECG is 16.7:1 for any event. Other univariate predictors included peak VO₂, standard QRS duration >120 msec, past history of sustained VT, and sex; these variables were not significant on multivariate analysis.

**Discussion**

In the present study, we examined whether an SAECG, a technique previously shown to be predictive of sudden death in patients with coronary artery disease, could provide similar prognostic information in patients with nonischemic dilated cardiomyopathy. We prospectively followed 114 patients with dilated cardiomyopathy who presented to our clinic over an
18-month period. From this study, several significant observations can be made.

The most important finding is that an abnormal SAECG can identify those patients with dilated cardiomyopathy who have the worst prognosis and who are at the greatest risk for sudden death. Only 39% of the patients with an abnormal SAECG did not have a significant event, defined as death or VT at 1 year. This was significantly worse than patients with a normal SAECG or bundle branch block who had a 1-year event-free rate of 95% and 88%, respectively. Our findings support those of Ohnishi et al,26 who describe a
high incidence of prospective arrhythmias and sudden death in 54 patients with a dilated cardiomyopathy and abnormal SAECG defined as a filtered QRS duration >120 msec or root-mean-square voltage <20 μV. Previous studies by Meinertz et al\textsuperscript{27} and Middlekauff et al\textsuperscript{28} had not found SAECG to be predictive of sudden death or ventricular arrhythmias. However, these studies used smaller patient populations and different criteria for an abnormal SAECG.

Meinertz et al studied 30 patients with nonischemic dilated cardiomyopathy, only one of whom had an abnormal SAECG. Seven deaths occurred in the 11 months of follow-up, and five of these deaths were from heart failure. Although they concluded that the SAECG was not predictive of sudden death, the number of outcomes was too small to reach any firm conclusion. Moreover, their study was similar to the present study in that the greatest risk to patients with a nonischemic cardiomyopathy and normal SAECG was progressive heart failure.\textsuperscript{27}

Middlekauff et al studied 22 patients with a dilated cardiomyopathy in whom three patients had abnormal SAECG by criteria that required a filtered QRS duration >120 msec, plus either a root-mean-square voltage <20 μV or low-amplitude signal duration >40 msec. Patients with bundle branch block were not analyzed separately. Five sudden deaths occurred. The average filtered QRS duration and root-mean-square voltage for these patients are not reported. Analysis was performed using data derived from patients with coronary artery disease as well as with nonischemic cardiomyopathy.\textsuperscript{28}

In our study, we also describe a significantly higher incidence of past ventricular arrhythmias in patients with an abnormal SAECG compared with patients with a normal SAECG. These findings confirm our previous report in which 83% of patients with a dilated cardiomyopathy who presented with a sustained ventricular arrhythmia had an abnormal SAECG versus 14% patients without a past history of sustained ventricular arrhythmias.\textsuperscript{20} Thus, SAECG can be used to identify patients with nonischemic congestive cardiomyopathy who have both past and prospective episodes of sustained ventricular arrhythmias.

Prospective adverse events in patients with abnormal SAECG were not clustered in any one etiologic subgroup, implying a common mechanism for arrhythmia generation. Interstitial fibrosis and hypertrophy frequently are seen on endomyocardial biopsies in patients with dilated cardiomyopathy. This can result in abnormal impulse conduction. SAECG may be helpful by noninvasively identifying those individuals with slowest ventricular activation and thus an underlying electrophysiological substrate that predisposes to ventricular arrhythmias.

Slowed ventricular activation manifested by a prolonged filtered QRS duration and presence of low-level late potentials appears to be a critical component of the arrhythmogenensis rather than a reflection of the severity of the disease. In our study, patients with an abnormal SAECG were comparable to patients with a normal SAECG in regard to left ventricular ejection fraction, peak exercise oxygen consumption, resting hemodynamic measurements, and NYHA functional classification. Thus, all parameters used to grade the severity of myocardial dysfunction were similar.

The presence of bundle branch block in our study was associated with more frequent past and prospective

---

**TABLE 4. Clinical Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Normal SAECG</th>
<th>Abnormal SAECG</th>
<th>Bundle branch block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>2 (3)</td>
<td>2 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0 (0)</td>
<td>5 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urgent transplants (No.)</td>
<td>3 (4.5)</td>
<td>1 (5)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia (No.)</td>
<td>0 (0)</td>
<td>4 (20)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Nonurgent transplant (No.)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Total dead or with sustained ventricular tachycardia (No.)</td>
<td>2 (3)</td>
<td>11 (55)</td>
<td>4 (14.3)</td>
</tr>
</tbody>
</table>

SAECG, signal-averaged ECG.

Values in parentheses indicate percentages.

---

**TABLE 5. Signal-Averaged ECG Measurements in Patients With an Abnormal Tracing With and Without Significant Adverse Event**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Good outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>13</td>
</tr>
<tr>
<td>Filtered QRS duration (msec)</td>
<td>128±15 121±7</td>
</tr>
<tr>
<td>RMS 40</td>
<td>37±11</td>
</tr>
<tr>
<td>Duration RMS &lt;40 μV (msec)</td>
<td>31±28</td>
</tr>
</tbody>
</table>

RMS 40, root-mean-square 40.

Adverse events are prospective ventricular tachycardia, death, or urgent transplant.

---

**TABLE 6. Clinical Characteristics of Subjects With Adverse Outcome Versus Those With Good Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Adverse outcome</th>
<th>Good prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>23</td>
<td>91</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49±14</td>
<td>47±15</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.1±0.6</td>
<td>2.5±0.8*</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>18±8</td>
<td>23±9*</td>
</tr>
<tr>
<td>VO₂ (mL/kg/min)</td>
<td>12.4±5.0</td>
<td>15.3±5.6*</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>22±8</td>
<td>19±10</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>1.9±0.4</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>7±4</td>
<td>10±6*</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association.

*p<0.05.
episodes of ventricular arrhythmias. In this study, all patients with bundle branch block who prospectively had VT had left bundle branch block. Two of the four who required urgent transplant had a left bundle branch block. Prior studies have reported bundle branch block to be an independent poor prognostic factor for patients with dilated cardiomyopathy.29,30 It has been hypothesized that presence of bundle branch block infers a diffuse degenerative disease of the myocardium and thus more extensive disease. Alternatively, it may simply imply damage to the His-Purkinje system because parameters used to measure disease severity (i.e., ejection fraction, resting hemodynamic measurements, and exercise capacity) were comparable in patients with bundle branch block and those with normal SAECG.

Although in this study we presume that sudden death results from ventricular arrhythmia, prior studies suggest that the mechanisms for sudden death in patients with heart failure are diverse, with 53% of patients actually succumbing to bradyarrhythmic events and only 38% to ventricular arrhythmias.31 Sudden deaths in our study occurred out of hospital with none of the patients undergoing autopsy. Therefore, we cannot exclude bradyarrhythmias, electromechanical dissociation, or fatal embolic events in these patients. However, the fact that we were able to prospectively identify patients who had VT suggests that the SAECG is more than just a marker for diffuse myocardial disease.

The mortality rate in our study appears surprisingly low with a 1-year mortality of 13%. Mortality rates for patients with dilated cardiomyopathy have ranged from 11% to 48%3-5,30,32-36. In 1983, Franciosa et al3 reported a 1-year mortality of 23% for patients with dilated cardiomyopathy. The majority of these patients were not receiving vasodilator therapy, which has recently been shown to significantly prolong survival in patients with heart failure.32,38 Cardiac transplantation also was not widely available at the time of that report. Analysis performed using urgent transplant as an end point in our study raises the 1-year mortality to 20%. Thus, the improvement in our survival may be accounted for by the recent advances in the therapy of heart failure. Similar to Franciosa et al, Likoff-Jessup et al also reported better survival in patients with dilated cardiomyopathy than in patients with coronary artery disease. Thus, our excellent survival is not inconsistent with past reports.

The incidence of sudden death in our study also was low, with only five sudden deaths in the 114-patient cohort. The incidence of sudden death in patients with dilated cardiomyopathy in past reports has ranged from 4% to 88%3-5,33-35,39. Our experience is similar to that of Maskin et al,39 who described a 4% incidence of sudden death despite 71% incidence of nonsustained VT on Holter monitoring. Frequent monitoring of electrolyte and digoxin levels may have helped to decrease the incidence of sudden death in our population. Moreover, 100 of our patients had angiographically normal coronary arteries, and ischemia was unlikely to contribute to arrhythmias in our patients. In some of the prior studies, coronary anatomy was not as well defined, and in some studies patients with coexistent coronary artery disease were included. Widespread use of angiotensin converting enzyme inhibitors40 and treatment of only symptomatic arrhythmias may also have helped to limit our incidence of sudden death.41

Results of the multivariate analysis demonstrate that an abnormal SAECG is an independent predictor of death in patients with dilated cardiomyopathy. This is the first study to demonstrate this finding. NYHA

### Table 7. Univariate and Multivariate Analysis: Prediction of Death, Urgent Transplant, or Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal SAECG</td>
<td>0.0001</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.0009</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak VO₂</td>
<td>0.02</td>
<td>0.82</td>
</tr>
<tr>
<td>Prior history of ventricular tachycardia</td>
<td>0.02</td>
<td>0.32</td>
</tr>
<tr>
<td>Standard QRS &gt;120 msec</td>
<td>0.03</td>
<td>0.17</td>
</tr>
<tr>
<td>Sex</td>
<td>0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.06</td>
<td>0.62</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>Antiarrhythmic drug use</td>
<td>0.21</td>
<td>0.37</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>0.29</td>
<td>0.68</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>0.77</td>
<td>0.40</td>
</tr>
<tr>
<td>Age</td>
<td>0.94</td>
<td>0.17</td>
</tr>
</tbody>
</table>

SAECG, signal-averaged ECG; NYHA, New York Heart Association.
classification also was found to be an independent variable confirming earlier reports.\textsuperscript{3,30,35} Surprisingly, neither left ventricular ejection fraction nor peak exercise oxygen consumption, the two variables that best quantitate the central and peripheral components of heart failure, were found to be independent predictors. Univariate analysis did demonstrate significance for peak VO\textsubscript{2}. Moreover, both of these variables were significantly lower in patients who had an adverse event defined as death, VT, and/or urgent transplant.

**Study Limitations**

The study is limited in that a complete electrophysiological evaluation was not done. Ambulatory Holter monitoring and electrophysiological testing were not routinely performed. However, prior studies suggest that Holter monitoring and electrophysiological testing are not predictive of sudden death in these patients.\textsuperscript{4-8}

Another criticism of this study is that the SAECG was most frequently abnormal due to increased filtered QRS duration. Therefore, one could argue that not much additional information is gained over surface ECG. However, studies in patients with coronary artery disease have shown that the filtered QRS duration is a better predictor of VT than QRS duration on standard ECG.\textsuperscript{42} Twenty percent of our patients with an abnormal SAECG had a normal filtered QRS duration. Moreover, results of multivariate analysis indicate that QRS duration from standard ECG was not an independent prognostic indicator.

Another potential limitation is that SAECGs in those patients receiving antiarrhythmic agents were obtained on therapy. Use of these agents in the 14 patients may have served to increase QRS duration. However, analysis of the data with patients receiving antiarrhythmic drugs excluded did not alter 1-year event-free rates. Moreover, multivariate analysis performed with antiarrhythmic drug use included as a variable demonstrated that it was not a significant independent predictor of survival (\(p=0.37\)).

Inclusion of patients with past history of ventricular tachycardia may be viewed as a limitation. However, exclusion of these patients would not significantly alter our results but instead actually strengthen them. Exclusion of the patients in the bundle branch block group with past history of ventricular tachycardia would increase significantly 1-year event-free survival from 75% to 89%. In the normal SAECG group, 1-year event-free survival would be unchanged at approximately 90%. However, in the abnormal SAECG group, 1-year event-free survival would decrease further from 39% to 25%. Statistical analysis performed using past history of ventricular tachycardia as a variable demonstrated it to be a univariate but not a multivariate predictor.

**Clinical Implications**

The results of this study have several important clinical implications. With the ever-expanding list of prospective cardiac transplant candidates, it is important to develop tools that will effectively risk stratify patients. SAECG appears to be a promising tool. First, it identifies a group of patients with nonischemic dilated cardiomyopathy who have an exceedingly low risk for future ventricular events. Indeed, patients with a normal SAECG have an extremely good prognosis (95% at 1 year) with their greatest risk for death being progressive heart failure. Prior reports have described the major threat to survival in patients with preserved exercise capacity as sudden death.\textsuperscript{43-45} Thus, a patient with a dilated cardiomyopathy who has a normal SAECG and relatively preserved exercise capacity (i.e., VO\textsubscript{2} >14 ml/kg/min) should have an excellent 1-year survival.\textsuperscript{46} Second, patients at high risk for death and/or VT are identified by the SAECG. Confirmatory studies are needed followed by clinical trials to establish appropriate antiarrhythmic therapy with drugs and/or devices. How best to design such a trial remains to be determined. Use of electrophysiology testing to define appropriate antiarrhythmic therapy generally has not been successful in this patient population.\textsuperscript{46,47} Moreover, the proarrhythmic effects of antiarrhythmic drugs are increased in patients with heart failure,\textsuperscript{41} although low-dose amiodarone may have a beneficial effect.\textsuperscript{48,49} Implantation of cardiac defibrillators is costly and not without significant mortality and morbidity in this ill population. Use of the SAECG may identify a subset of patients who may most benefit from implantable defibrillators. This would help to contain costs and focus therapy on those who most need it. Third, this study identifies a marker of sudden death in patients with dilated cardiomyopathy. No other variable in patients with significant left ventricular dysfunction has been found to predict VT and sudden death.

The problem of sudden death, the mechanisms that produce it, and the means to prevent it remain a critical area for future research. SAECG will provide a powerful noninvasive tool in future research efforts to risk stratify patients with heart failure.

**Acknowledgments**

We gratefully acknowledge the expert technical assistance of Andrea Rein, RN, MSN, Nancy Britton, RN, MSN, Karen Fleming, RN, Elizabeth Powers Byrd, RN, MSN, Edward Gracey, PhD, and Anita Armellini.

**References**


Mancini et al SAECG in Dilated Cardiomyopathy 1091


Prognostic value of an abnormal signal-averaged electrocardiogram in patients with nonischemic congestive cardiomyopathy.

D M Mancini, K L Wong and M B Simson

_Circulation_. 1993;87:1083-1092
doi: 10.1161/01.CIR.87.4.1083
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/4/1083

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/