List of Titles

Technical Information Report

AAMI TIR23:1999

Signal averaging

AAMI Association for the Advancement of Medical Instrumentation

AAMI TIR No. 23:1999

Signal averaging

Approved 15 March 1999

Abstract: The signal-averaged electrocardiogram (SAECG) facilitates noninvasive recording of low-amplitude cardiac signals such as ventricular late potentials. The SAECG has been used to predict life-threatening ventricular tachyarrhythmias in patients after acute myocardial infarction and with nonischemic dilated cardiomyopathy and to screen for inducible ventricular tachycardia in patients with unexplained syncope and with nonsustained ventricular tachycardia. This technical information report focuses on currently accepted methodology and clinical applications of the SAECG.

Key words: signal-averaged electrocardiogram (ECG), ventricular tachycardia, sudden cardiac death, electrophysiologic study, syncope, myocardial infarction, cardiomyopathy, atrial fibrillation

List of Titles

Published by the

Association for the Advancement of Medical Instrumentation
1110 N. Glebe Road, Suite 220
Arlington, VA 22201-5762

Printed in the United States of America

ISBN 1-57020-129-3

AAMI TECHNICAL INFORMATION REPORT

A Technical Information Report (TIR) is a publication of the Association for the Advancement of Medical Instrumentation (AAMI) Standards Board that addresses a particular aspect of medical technology.

Although the material presented in a TIR may need further evaluation by experts, there is value in releasing the information because of the immediate need for it by the industry and the professions.

A TIR differs markedly from a standard or recommended practice, and readers should understand the differences among these documents.

Standards and recommended practices are subject to a formal process of committee approval, public review, and resolution of all comments. This process of consensus is supervised by the AAMI Standards Board and, in the case of American National Standards, the American National Standards Institute.

A TIR is not subject to the same formal approval process as a standard. However, a TIR is approved for distribution by a technical committee and the AAMI Standards Board.

Another difference is that although both standards and TIRs are periodically reviewed, a standard must be acted upon—either reaffirmed, revised, or withdrawn—and the action formally approved usually every 5 years but at least every 10 years. For a TIR, AAMI consults with a technical committee about 5 years after the publication date (and periodically thereafter) for guidance on whether the document is still useful—that is, to check that the information is relevant or of historical value. If the information is not useful, the TIR is removed from circulation.

A TIR may be developed because it is more responsive to underlying safety or performance issues than a standard or recommended practice, or because achieving consensus is extremely difficult or unlikely. Unlike a standard, a TIR permits the inclusion of differing viewpoints on technical issues.

CAUTION NOTICE: This AAMI Technical Information Report may be revised or withdrawn at any time. Because it addresses a rapidly evolving field or technology, readers are cautioned to ensure that they have also considered information that may be more recent than this document.

Contents

Tables

Figures

Committee representation

Association for the Advancement of Medical Instrumentation
Electrocardiograph Committee

This technical information report (TIR) was developed by the ECG/Signal Averaging Working Group of the AAMI Electrocardiograph Committee. Committee approval of the TIR does not necessarily imply that all committee members voted for its approval.

At the time this document was balloted, the **AAMI Electrocardiograph Committee** had the following members:

Cochairs:	James J. Bailey, MD David Mortara, PhD
Members:	James J. Bailey, MD, National Institutes of Health Alan S. Berson, PhD, National Heart, Lung, and Blood Institute Robert E. Bruce, Medicomp David Daly, U.S. Food and Drug Administration Arthur R. Eddy, Jr., ConMed Corp. Stacy Gehman, Quinton Instrument Co. Paul Lander, University of Oklahoma Health Sciences Center George Moody, Massachusetts Institute of Technology David Mortara, PhD, Mortara Instrument Inc. Shankara Reddy, PhD, GE-Marquette Medical Systems William Saltzstein, Medtronic Physio-Control Corp. Jonathan Steinberg, MD, St. Luke's Roosevelt Hospital Roy D. Wallen, Pure Pulse Technologies
Alternates:	Robert J. Cangelosi, U.S. Food and Drug Administration

At the time this document was balloted, the committee's **ECG Signal Averaging Working Group** had the following members:

Cochairs	Paul Lander William Saltzstein Jonathan Steinberg, MD
Members:	Edward J. Berbari, PhD, Indiana University Alan Berson, PhD, National Heart, Lung, and Blood Institute Stacy Gehman, Quinton Instrument Company Paul Lander, University of Oklahoma Health Sciences Center Shankara Reddy, PhD, GE-Marquette Medical Systems William Saltzstein, Medtronic Physio-Control Corp. Craig Sellers, Spacelabs Burdick Mike Simson, MD, University of Pennsylvania Jonathan Steinberg, MD, St. Luke's Roosevelt Hospital Jerry Sweeten, Plastics One Inc. Sandy Weininger, U.S. Food and Drug Administration
Alternates:	Carole Carey, U.S. Food and Drug Administration

Acknowledgement

The ECG Signal Averaging Working Group gratefully acknowledges the contributions of former cochair Edward Berbari, PhD, and contributor Eric Chan, PhD.

NOTE—Participation by federal agency representatives in the development of this report does not constitute endorsement by the federal government or any of its agencies.

Signal averaging

1 Scope

Signal averaging of the electrocardiogram (SAECG) was devised 25 years ago to reveal low-amplitude cardiac signals in the microvolt range on the body surface. It was originally used to detect His-Purkinje activity (A.1). However, in the next decade the methods for SAECG were refined and developed to determine the full extent of ventricular activation with the object of revealing delays relating to electrical instability of the ventricular myocardium.

The purpose of this report is to provide an understanding of the fundamental principles underlying SAECG methodology, to define terminology, and to review its potential for clinical application. It includes a discussion of some of the major pitfalls that must be avoided. This report is directed partly to those who have an interest in the clinical use of the SAECG but also to those who are considering the development of SAECG methodology in a medical device. The following topics are covered:

a) device architecture for data acquisition and processing;
b) beat selection and alignment;
c) ensemble averaging;
d) filtering, lead combination, and measurement;
e) clinical applications and emerging uses;
f) a list of publications for further reference;
g) terminology.

2 Definitions

For the purposes of this technical information report, the following definitions apply.

2.1 bandpass filter: A filter that will pass frequencies within a desired range but will attenuate all other frequencies (e.g., a 40– to 250–Hz filter would attenuate frequencies below 40 Hz and above 250 Hz).

2.2 baud rate: The number of bits per second that can be transmitted in a given computer system.

NOTE—When information is transmitted between two computer systems, each must be set to the same baud rate.

2.3 bidirectional filter: A type of digital filter that filters the signal in a forward direction from its beginning to its midpoint and then filters from the end of the signal in a backward direction to the same midpoint.

2.4 Butterworth amplitude filter: A type of filter known for its filter quality on small signals; the filter of choice for the vector magnitude and late potential detection.

2.5 corner frequency: The frequency or frequencies selected to define a filter band (e.g., 40– to 250–Hz Butterworth filter).

2.6 FFT: Fast Fourier Transform is a method by which a segment of time series data can be evaluated for its frequency components.

2.7 fiducial point: A reliable, stable reference point that allows multiple beats to be aligned for averaging.

NOTE—One fiducial point commonly used for SAECGs is the onset of the QRS or the time of maximum slope of the QRS.

2.8 filter: A device or software algorithm that passes information within signals of certain frequencies or frequency ranges while attenuating others.

2.9 finite impulse response (FIR) filter: A type of filter that relies only on previous input to generate its present output.

2.10 high pass filter: A filter that attenuates frequencies below a specified frequency (e.g., a 40–Hz high pass filter would attenuate all frequencies below 40 Hz).

2.11 high resolution: Having the ability to acquire, resolve, and analyze data in fine increments.

2.12 LAS 40: An abbreviation for low–amplitude signal below 40 uV.

NOTE—It references the duration of the signal below 40 uV measured on the vector magnitude.

2.13 low pass filter: A filter that attenuates frequencies above a specified corner frequency (e.g., a 250–Hz low pass filter would attenuate all frequencies above 250 Hz).

2.14 microvolt (uV): 1 /1,000,000 of a volt or 1/1,000 of a millivolt; represents 100th of a millimeter at standard ECG gain.

2.15 millivolt (mV): 1/1,000 of a volt.

2.16 negative predictive value: The probability that the patient does not have the disease if the test is negative.

2.17 noise: Any signal other than what is wanted.

NOTE—In signal averaging, noise consists of electrical signals, typically between 1 and 20 microvolts, contained in a surface ECG recording which originate primarily from electrode movement, muscular contraction, respiratory movement, and electronic equipment. Since noise signals occur randomly, attenuation occurs with the averaging process. The square root of the number of beats averaged represents the improvement in the signal-to-noise ratio (e.g., if 100 beats are averaged, the signal-to-noise ratio has been improved by a factor of 10).

2.18 orthogonal leads: Leads that are perpendicular to each other.

2.19 positive predictive value: The probability that the patient has the disease if the test is positive.

2.20 root mean square (RMS) voltage: The 'energy' content in microvolts contained under the curve or any selected portion of the curve created by the vector magnitude.

2.21 signal-averaged electrocardiogram (SAECG): The averaging together of multiple ECG cycles (see signal averaging).

NOTE—The cardiac electrical activity may then be processed in a variety of ways (e.g., time domain, frequency domain, etc.) for further analysis.

2.22 signal averaging: Using computer-based processing techniques, multiple R- (or P-) wave samples are averaged together to form one highly refined R- (or P-) wave complex.

NOTE—Nonrepetitive, random signals such as electrical noise are attenuated or eliminated.

2.23 vector magnitude: A graph created by taking the square root of the sum of $X^2 + Y^2 + Z^2$ where X represents the signal-averaged and filtered data from the X lead, Y the data from the Y lead, and Z the data from the Z lead.

NOTE—A vector summation of the high-frequency information is obtained from all leads. Squaring any signal always results in its being positive.

2.24 ventricular late potentials: Low-amplitude, high-frequency electrical signals which are found in the terminal portion of the QRS complex and which last a variable time into the ST segment.

NOTE—They appear to correspond to delayed, fragmented ventricular activation which has been observed with epicardial and endocardial electrogram recordings in patients with ventricular tachycardia. It is theorized that late potentials have the same anatomic substrate as reentry tachycardia.

2.25 X lead: A bipolar lead used for signal-averaged ECGs in which X+ is placed in the fourth intercostal space, midaxillary line, left side, and X- is in the same position on the right side.

2.26 Y lead: A bipolar lead used for signal-averaged ECGs in which the Y+ is placed on the proximal left leg and Y- is placed on the manubrium.

NOTE—Alternatively, the standard V-3 position for Y+ and left of the sternum or the suprasternal notch for Y- have been referenced in literature.

2.27 Z lead: A bipolar lead used for signal-averaged ECGs in which the Z+ lead is placed in the standard V-2 position and the Z- is in a comparable position on the posterior chest.

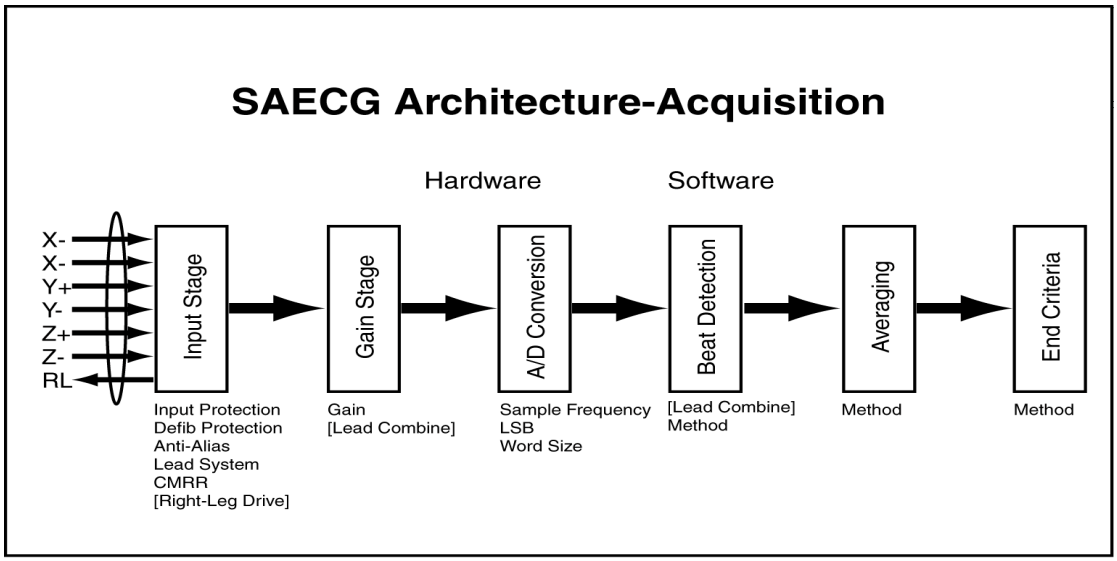
3 State of the art of current SAECG device design

3.1 Introduction

All SAECG instrumentation currently being marketed are of similar construction and design. They vary primarily in the techniques used for signal processing, waveform measurements, and noise measurements. This section details a common architecture to be used for comparative purposes and summarizes the attributes of the current state of the art based on this architecture. Information content was contributed from major SAECG vendors.

3.2 Architecture

Figure 1 is a representative architecture of current SAECG devices. Note that it shares many common attributes with standard 12-lead ECG instrumentation.



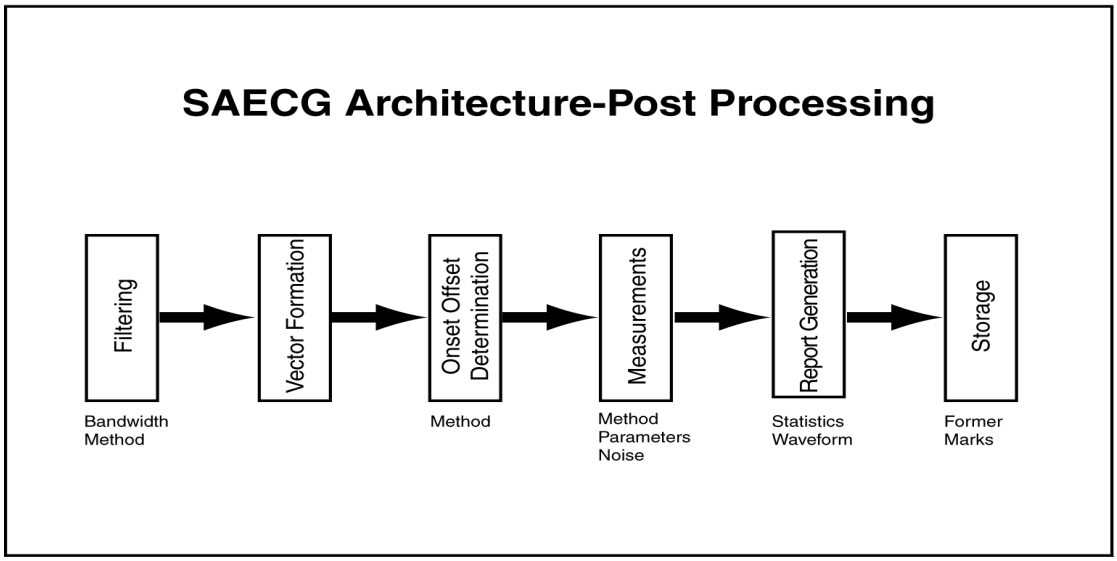


Figure 1—Representative architecture of current SAECG devices

3.3 Comparative table of specifications

Specification	Minimum	Typical	Maximum	Notes
Input Stage				
Input Protection	±6KV		±20KV	ESD, etc
Defibrillation Protection	Yes	360J		
Anti-Alias	Yes	300Hz		
RL Drive	None	Yes		
CMRR	120 dB	150 dB		RTI per AAMI ECG Spec, IEC 601-1, IEC 601-1-2
Electrodes		Ag/AgC1		
Lead System		Bipolar X, Y, Z; Frank X, Y, Z.		
Gain	100	1000	8000	RTI system gain
Lead Combine		Hardware; Software.		
A/D Conversion				
Sample Frequency	1000	1000	2000	Samples/second
LSB	0.3 µV	2.5 µV	2.5 µV	
Word Size	12 Bits	16 Bits	22 Bits	
Interchannel delay	0	10 µS	50 µS	
Signal Averaging				
Beat Alignment*		Correlation of QRS		
Exclusion of beats		Mismatch of QRS	Ectopic beats; Shorter R-to-R intervals; Wider QRS; Excessive Noise	
End Criteria Method		Number of beats	Noise level*	
Measurements/ Late Potential Parameters**		FQRSd, LASd, RMS40		
Report Generation				
Measurements and Statistics		FQRSd, LASd, RMS40; Number of beats; Noise level*.		
Waveforms		Unfiltered X, Y, Z; Filtered X, Y, Z; Vector magnitude		
Storage				
Data Content		Unfiltered X, Y, Z; Filtered X, Y, Z; Vector magnitude; Fiducial points; Statistics; Measurements	Raw Data	
Media		Floppy diskette;	Floppy diskette; Hard disk; Transmit	

* These features are elaborated further in section 3.4.

** ESD = electrostatic discharge; RTI = referred to input; FQRSd = filtered QRS duration; LASd = low-amplitude signal duration under 40 uV from the filtered QRS offset; RSM40 = root mean squared voltage in the terminal 40 milliseconds (ms) of the filtered QRS.

3.4 Summary of beat alignment and measurement methods

Beat Alignment: Incoming beats are matched with a template or a seed beat. Either the signals in the entire QRS complex or a number of equally spaced samples within the QRS are used for matching and beat alignment (cross-correlation). Both time- and frequency-domain correlation methods have been employed for this purpose. In addition, abnormally conducted beats and noise spikes may also be discarded based on the R-to-R intervals and the measured QRS duration.

Noise Measurement: Noise is measured in a 40-ms window in the ST-T segment in the averaged unfiltered or filtered ECG signals or the vector magnitude waveform. It is computed and reported as the mean value, RMS value, or the standard deviation of the signal in this window. Unit of measurement is micro-Volts (μV)

Fiducial Point Delineation: Onset and offset (fiducial points) of the filtered QRS waveform are determined typically using the vector magnitude waveform. In some systems, individual lead (X, Y, Z) filtered waveforms are also used. Thresholds for these delineations are based on the measured noise level(s). The threshold for filtered QRS offset is typically set as either 2 times the mean voltage in the noise window or mean voltage plus 2 times standard deviation of voltages in the noise window. In some systems, the filtered QRS onset is the same as the unfiltered QRS onset, while in others it is set at a point where the voltage equals 3 times the average noise voltage.

4 Selection and alignment of normal sinus rhythm beats for ensemble averaging

4.1 Overview

Before ensemble averaging, a representative sinus rhythm QRS complex must be chosen. This is known as the *template* beat. Each subsequent incoming beat is first detected electronically. The beat is then aligned precisely with the template to obtain a synchronized, fiducial point for averaging. Acceptance of each beat is subject to accuracy of alignment and beat-type tests.

4.2 Selecting a normal sinus rhythm beat as a "template"

A "template" beat must be selected before ensemble averaging begins. The template can be selected manually from a graphic display or automatically via a computer algorithm. Manual selection is performed visually, with the user selecting a normal sinus rhythm complex of a typical morphology and low noise. Automatic selection must contend with the morphology variations due to respiration, fluctuating noise levels which may have a molding effect on the ensemble average (A.2), and the presence of premature ventricular contractions (PVCs).

In one published approach (A.3), signals from the X, Y, and Z leads are first low pass filtered, then differentiated as

$$dX_i = X_{i+2} + 2X_{i+1} - 2X_{i-1} - X_{i-2}$$

where x_i is the low pass filtered signal and dx_i is the 5-point central difference at time instant 'i' for one lead. The three low pass filtered, differentiated signals are combined into an absolute spatial velocity (ASV) as

$$ASV_i = \|dX_i\| + \|dY_i\| + \|dZ_i\|$$

During the processing of the first 8 seconds of data, two threshold values (Threshold_1,and Threshold_2) are established from the ASV. Threshold_1 is at 40% of the maximum value of the ASV, and Threshold_2 is at 12% of the maximum plus the average of the background noise. Using Threshold_1, probable QRS complexes are detected, while Threshold_2 is used to delineate their onsets and offsets. If the duration of a detected complex is greater than 60 ms, it is considered a QRS complex. Choice of the template beat is based on analyses of rhythm analysis and QRS durations of the detected beats. The beat with the shortest QRS duration and most likely to be of sinus origin is chosen as the template beat.

In an alternative approach, each incoming QRS is analyzed, the dominant beat type is identified, and a representative complex is selected as the template. In another system, four beats are cross-correlated to determine the most common morphology. The beat with the highest correlation with others of the same type is selected as the template.

In summary, a small number of beats are acquired and the QRS events are detected, either in hardware or in software from the digital record**.** The events are parsed to obtain a representative normal sinus rhythm (NSR) beat. The procedure may use measurements of morphology similarity (cross-correlation, area), rhythm (RR interval), and

QRS duration to determine which beat or *processed combination of beats* will serve as the representative NSR (template) complex. Events such as arrhythmic or noisy beats are excluded in the second stage of processing. Typically, this complex is then presented graphically to the user who may accept it as the template or alternatively may manually select a different beat.

4.3 Beat alignment techniques

Each incoming beat is compared with the template beat in order to obtain a *fiducial,* or alignment, timing reference. The incoming beat is matched to the template one sample point at a time through a *sweep range* (typically 20 ms), centered at the initial crude electronic QRS detection point. The correlation coefficient between the template and incoming beat is computed at each point in the sweep range. The point of best alignment is found typically by computing the correlation coefficient between the template and the incoming beat, defined by

$$\rho_\tau = \frac{\sum_{i=\tau-M/2}^{\tau+M/2} x_i y_i}{\sqrt{\sum_{i=\tau-M/2}^{\tau+M/2} x_i^2}\sqrt{\sum_{i=\tau-M/2}^{\tau+M/2} y_i^2}}$$

where x_i and y_i are the sample values of the template and the latest beat, respectively, and M is the width of the portion of the QRS used for alignment. This is typically from the onset to just after the peak of the QRS. The beat alignment point is the time of the maximum value of ρ_τ for each discrete computation in the sweep range. A threshold value of $\rho = 0.99$ is typically used as the beat acceptance criterion. The potential alignment error, expressed in milliseconds, is often referred to as *trigger jitter.* Ideally, trigger jitter is restricted to +/- one sampling interval (0.5–1.0 ms). It acts as an equivalent low pass filter, smoothing high-frequency components of the ensemble average. This effect has been analyzed extensively (A.4). Typically, only one lead (frequently the X lead) is used for this calculation.

Variations on this basic technique have been used. The template and incoming beats may be filtered to remove low-frequency artifacts, such as baseline wander and amplitude modulation of the ECG caused by respiration and changing heart position. Selected Fourier coefficients (e.g., those above 20 Hz) of the template and incoming beat may be used in place of the time domain waveforms. In addition, earlier methodologies did not use correlation. Instead the mean-squared error between the template and incoming beat was computed at each point in the sweep range, with the minimum defining the fiducial point.

4.4 Rejecting nonsinus rhythm beats

It can be a nontrivial task to reject beats of nonsinus origin from the ensemble average. Correlation is amplitude insensitive, resulting in potentially high correlations with noise spikes. PVC's may have a very close morphology to normal sinus rhythm beats. Fusion beats may be identical to normal sinus rhythm beats in the period of the QRS used for alignment.

To avoid accepting events that are not low noise, normal sinus rhythm beats into the ensemble average, some form of postcorrelation beat type control is needed. This usually consists of a comparison of the area (i.e., integral) of the preliminarily accepted QRS with the template beat QRS. Either the entire QRS period is used, or the first and second parts of the QRS are compared separately. In addition, some form of high pass filtering (e.g., a simple difference) is useful for accentuating distinguishing features of normal and abnormal QRS complexes.

5 Ensemble averaging

5.1 Overview

Ensemble (signal) averaging has been universally used to estimate late potentials in the high resolution ECG. The signal average, $\bar{x}(t)$, is formed by summation of all accepted beats in the ensemble where i is the beat index and R is the number of beats in the ensemble. The process assumes a deterministic, repetitive cardiac signal component, $s(t)$, and a Gaussianly distributed noise component, $n(t)$, in the set of x_i.

$$\bar{x}(t) = \sum_{i=1}^{R} x_i(t) / R = s(t) + \bar{n}(t) / \sqrt{R}$$

5.2 Endpoint of signal averaging: quality control

Either a fixed number of beats or a target averaged noise level is used to determine the size of the ensemble. The latter has the advantage that a guaranteed final noise level (and hence quality of the signal-averaged ECG [SAECG]), is achievable. The *signal variance method* gives the highest accuracy noise measurement, considered from the central limit theorem. The noise power (or variance), N_R, of the signal average is given by

$$N_R = \left(\sum_{i=1}^{R} (x_i - \mu_i)^2 / R - \left(\sum_{i=1}^{R} (x_i - \mu_i) / R \right)^2 \right) / R$$

where x_i and μ_i are the sample and mean values for beat i, respectively, in a preselected noise window. This noise window is ideally placed in the ST segment, away from the terminal QRS and T wave periods. It is typically 50 ms in duration. Approximately 10 evenly spaced samples (e.g., every 5 ms) are adequate for characterization of the signal variance in the noise window. A disadvantage of the signal variance method is its potential to overestimate noise levels because of beat-by-beat morphological changes in the ECG. This creates a sensitivity to the noise window position. This sensitivity can be greatly reduced by differentiating the ECG before measuring N_R.

Alternatively, noise can be measured directly from the final SAECG in either the filtered leads or the vector magnitude waveform. This method is simpler to compute but has greater variance. It is highly sensitive to the noise window position. Noise estimates can typically vary by ±300% with either the Gaussian noise distribution of the individual leads or the chi-square noise distribution of the vector magnitude. The central limit theorem suggests that this limitation is overcome either by averaging the RMS amplitudes of several noise windows or by taking as large a noise window as is practicable (typically 40–70 ms).

It is a common practice to use the quietest 40-ms noise window that can be found from scanning the ST segment. The rationale for this is to be able to select a quiescent period without *a priori* knowledge of the QRS and T wave limits. However, this procedure may result in a significant underestimation of noise. If SAECG noise approximated an ergodic process, then random variations by a factor of up to 8 in the RMS value of 40-ms segments would be present. Using the lowest amplitude window would create a serious bias in the noise estimate. However, the situation is mitigated by the limited bandwidth of ECG noise. This would be particularly true of SAECG systems that performed significant smoothing of the high pass filtered ST segment. In that case, the 'quiescent' 40-ms window is more likely closer to the mean noise value. Some processing of overlapping 40-ms segments could be performed to locate a quiescent period. The resulting underestimate in noise amplitude could be compensated for by an averaging scheme using time-adjacent windows. These approaches have not been explored. The area of noise estimation requires further work before a robust industrial standard could be claimed.

Results of the two noise measurement techniques (i.e., signal variance and *mean* RMS amplitude of a noise window in the signal average) can be related to each other statistically but may vary significantly in individual cases (A.5).

5.3 Rejection of adversely noisy beats

It is advantageous to reject very noisy beats from the ensemble average. This avoids the possibility of creating artifactual late potentials and leads to a high fidelity average with the smallest number of beats. Noisy beat rejection can be incorporated into the averaging process by rejecting beats that cause N_R (the signal variance) to increase significantly, where R is the number of the current addition to the average.

6 SAECG analysis: digital filtering, lead combination, and measurements

6.1 Overview

After the SAECG has been computed, analysis of the data is performed in software. This analysis consists of digital filtering (to remove signals outside the band of interest), formation of the 3-lead vector magnitude, and the measurement of parameters from the vector magnitude waveform.

6.2 Digital filtering schemes

The purpose of digital filtering of the SAECG is to remove signal and noise energy in frequency bands outside that of the cardiac signal of interest. A bandpass filter is typically used. High-frequency energy is reduced to attenuate noise. The low pass section typically has a -3 dB cutoff frequency of 250 Hz and a second or fourth order roll-off. Low-frequency energy is reduced to eliminate the ST segment waveform and slow portions of the QRS complex. The high pass section typically has a -3 dB cutoff frequency of 40 Hz and a third or fourth order roll-off. Cutoff frequencies of 25 and 80 Hz have also been used widely (A.6).

The high pass filter section is of principal importance. The objective is to enable identification of the latest moment of ventricular activation. The premise is that activity below 40 Hz is associated with repolarization, while the activity above 40 Hz represents ventricular depolarization.

The desired characteristics of the high pass filter are as follows:

- separation in frequency of QRS/late potentials energy (20–250 Hz) and the ST segment (0–30 Hz);
- avoidance of spreading in time of QRS components (including late potentials);
- preservation of filtered QRS morphology (desirable, but not used clinically as of this publication).

All these requirements are not easily fulfilled with fixed frequency band digital filters. There are three distinct filtering strategies that have been employed with the SAECG that are discussed below.

6.3 Butterworth IIR filter, applied in a bidirectional mode

An infinite impulse response (IIR) filter can easily approximate the desired frequency response (i.e., a narrow transition interval between the stopband [0–30 Hz] and passband [40–250 Hz]). Due to nonlinear phase characteristics and ringing, the QRS morphology is heavily distorted, and the QRS is spread in time. However, the ringing can be confined to within the QRS if the filter is applied in a bidirectional mode (A.7). In this mode, the filter is run forward in time up to the midpoint of the QRS and then in reverse time from the T wave to the QRS midpoint. In this way, the endpoints of the filtered QRS are neither obscured nor shifted in time.

6.4 Spectral window filter

An alternative strategy is to define a zero-phase filter that directly modifies the complex coefficients of the Fourier spectrum of the SAECG. One approach is to use a modified Kaiser-Bessel function to approximate a 40-Hz high pass filter with an adequate transition interval characteristic (A.8). The QRS is spread in time by a few ms but its filtered morphology is preserved. If the cutoff frequency is extended to 55–65 Hz, no appreciable ringing of the QRS occurs with the modified Kaiser-Bessel function. The measured QRS limits obtained with this filter and the bidirectional Butterworth are comparable (A.9).

A second spectral window filter has been widely used (A.10). This filter similarly creates a transfer function to give the desired high pass characteristic. A low pass function is also implemented. In general, the resulting filtered QRS morphology is spread in time by up to 10 ms, compared to that obtained with the bidirectional IIR filtering method. The clinical significance of measuring the QRS under these conditions has been explored (A.11). Equivalence, or relative performance, of this spectral window and the bidirectional IIR filtering technique has been studied (A.7, A.9, A.11). These studies indicate that measurement criteria for each filtering process must be applied separately.

6.5 FIR filter

A third approach is to use a finite impulse response filter, designed for example by the minimax method (A.12). This filter spreads the QRS in time but has acceptable frequency discrimination between stopband and passband and minimal distortion of the filtered QRS in the linear phase sense (A.8).

6.6 Lead combination: vector magnitude waveform

The three resultant filtered leads are combined into a vector magnitude waveform, *VM(t)*, defined conventionally as

$$VM(t) = \sqrt{X^2(t) + Y^2(t) + Z^2(t)}$$

where *X*, *Y*, and Z represent the signal-averaged, digitally filtered leads. The vector magnitude waveform, as widely reported, makes no attempt to compensate for mechanical or electrical nonorthogonality or differences in interelectrode distances, resulting in systematic differences in the amplitudes among the XYZ leads.

6.7 SAECG measurements of late potentials

Measurements of the SAECG are based on determination of the QRS limits. The onset of the QRS is an electrophysiologically distinct event, occurring directly after activation of the Purkinje fibers. QRS onset is found in a manner similar to the approach used with the standard ECG. The absolute spatial velocity vector (differentiated SAECG)—or the high pass filtered SAECG—is computed. The QRS onset has been defined as the point where a significant increase in signal level occurs, comparing a 5-ms moving window with a reference level from a window positioned in the quiescent period of the PR interval. It should be noted that in the high resolution ECG, the PR interval is not isoelectric, as is conventionally assumed. Late atrial and conducting system activity are present. A potential inaccuracy may occur if the SAECG has been filtered with an IIR filter. This is due to P wave ringing that may obscure the QRS onset. Alternatively, the QRS onset may be calculated by considering the three *unfiltered* leads individually. The earliest detected QRS onset is then typically used.

The definition of QRS offset is technique dependent as opposed to an electrophysiologically distinct event. The underlying assumption is that the end of ventricular activation is defined as the latest moment of high-frequency QRS energy. Typically, a reference RMS noise level is measured in a 40-ms window, positioned in the filtered ST segment of the vector magnitude. A shorter window (e.g., of 5-ms duration) is then used, stepping backwards in time, until a three-fold increase over the reference noise level is obtained (A.13). When this condition is met, the center of the moving window defines the QRS offset. Variations on this theme have been used in SAECG systems (A.3). This involves the use of 1-ms steps, defining the QRS offset as the point where the mean voltage in a segment between 5-ms and 40-ms duration (typically 10-ms) exceeds twice the noise threshold, subject to a minimum of 0.5 μ (A.13).

A potential disadvantage of this class of method is susceptibility to triggering, on noise spikes in the ST segment, if the SAECG averaged noise level is low. A refinement of the above approaches has been proposed in response to this problem (A.14). Initially, a 40-ms-wide window is used to establish a rough, noise-insensitive estimate of the QRS offset, as described above. A retrospective search of the ST segment, using a window of 20-ms duration, is then started from 20 ms beyond the detected offset point. This procedure is repeated, halving the window duration with each iteration, until the latest instant of the QRS signal is detected. This approach achieves greater precision of the detected QRS offset and avoids false detections in the ST segment.

With knowledge of the QRS limits, three parameters have conventionally been measured from the filtered SAECG vector magnitude. These are

a) high-resolution QRS duration (including late potentials), defined as the period between the filtered QRS offset and onset (fQRS);
b) the RMS value of the terminal 40 ms of the QRS complex (RMS V40);
c) the duration of low-amplitude signal below 40 μV, ending at the QRS offset (LAS).

7 Clinical applications of SAECG

The signal-averaged electrocardiogram was introduced over two decades ago and has been used extensively in clinical investigation and clinical practice to study the duration of ventricular activation. A major advantage of the SAECG over standard ECG recording is the ability to record low-amplitude cardiac signals, in the microvolt range, which allows a more accurate measurement of ventricular activation delay, a prerequisite for ventricular reentry. This review focuses on currently accepted methodology, oriented towards the clinical interested reader. It presents clinical applications of the time-domain SAECG and highlights its development from research technique to office test.

7.1 SAECG methodology

Obtaining a signal-averaged ECG is performed in two steps: acquisition and analysis. The acquisition begins with a three-lead, uncorrected XYZ lead set. The XYZ signals are directed to low-noise biophysical amplifiers. The key features of these amplifiers are that they meet the standards for leakage current patient isolated equipment, and they must be defibrillation protected. As these amplifiers are differential, they must be able to limit 60-Hz electrical line interference that is often electrostatically coupled into the system.

The signals should be directed through a bandpass filter which attenuates both low and high frequencies within specified limits. For the SAECG, the bandwidth is 0.05–300 Hz. For practical purposes the 300 Hz low pass frequency is more than adequate for the SAECG. In Holter systems where there is a poor bandwidth at the higher frequencies, caution should be taken when these systems are used for late potential analysis. A frequency response less than 100 Hz may unduly distort, in a nonsystematic fashion, the SAECG (A.15).

The next step in the SAECG process passes the signals through an analog-to-digital (A/D) converter which transforms the time varying voltages to the digital domain of the computer. The sampling frequency is usually 1000 or 2000 times per second for each lead. The voltage resolution can be as little as 1 part in 4000 (a 12 bit A/D) or as high as 1 part in 65,000 (a 16 bit A/D). While the 16 bit resolution is superior, there is little difference in these systems from a clinical diagnostic perspective.

The first step in implementing the SAECG software is the detection and alignment of the QRS complexes. In some systems this is a completely transparent process for the user, while in others it is possible to tune the process to enable greater accuracy and flexibility in signal averaging. By considering the shape of the QRS, one can accomplish two things: (1) a more accurate detection of the QRS by eliminating ventricular premature depolarizations (VPDs), excessively noisy beats, and motion artifacts; (2) allow the system to finely align each QRS complex for the purposes of averaging. The most common method to incorporate the shape of the QRS is correlation. This process compares each incoming beat with a preselected template beat. In some commercial systems the user will select the template, while in others the computer will choose the template. In some cases the template is an average beat from the first 10 seconds of signal acquisition or it can be changed dynamically and be based on the signal average itself after the first 10 or 20 beats are averaged. This initial part of the signal averaging process could be considered a learning phase. If the template is automatically chosen, the learning process should be understood in order to avoid cases where premature ventricular beats may be included in the template learning process.

After the computer has detected and aligned a beat, it will be added point-by-point for each XYZ lead. Dividing the sum by the number of beats will then result in a set of averaged recordings. As each beat is added, the noise is reduced in the signal-averaged recordings due to the random nature of the noise. The signals which repeat on a beat-to-beat basis will emerge as the average of the noise goes to zero. This is the primary reason for using the signal-averaging method, because very low-level signals are usually masked in noise. Thus, standard ECG techniques are not adequate for recording these very low-level signals. Theoretically, the noise will decrease by the square root of the number of beats averaged. If 100 beats are averaged, then the noise will be reduced by a factor of 10. In practice, this is only approximate because the characteristics of the noise may vary over time. The most significant source of noise in the SAECG is the signal generated by the chest wall muscles during normal physiological processes such as breathing.

The initial SAECG studies used a predetermined, fixed number of beats, for the average (e.g., 200 or 300 beats per average). This proved to be unsatisfactory because each patient had his or her own noise and signal level characteristics. The most common approach used to terminate an average with a measurable and consistent performance is to measure the noise during the averaging process until some predetermined level is reached (A.16). Several approaches are used for measuring residual noise as the averaging process is performed, and it is not possible to directly compare noise voltage values from the different methods.

After one is assured that a high-quality, low-noise SAECG has been obtained from the patient, the next step is the analysis of the SAECG. The primary waveform analyzed for cardiac late potentials is the filtered vector magnitude which is derived from the averaged XYZ leads. Figure 2 shows the sequence of signal processing of the XYZ leads to arrive at the filtered vector magnitude. Panel A is a 3-second rhythm strip showing the individual XYZ leads at a typical amplitude and time scale which is familiar to the reader. Panel B has an expanded time (factor of 10) and amplitude scale (factor of 5) and is an averaged QRS complex for each lead. Note that at the end of each QRS, one can appreciate small deflections. These are the late potentials, but they are difficult to discern and quantify. Panel C shows each of these leads after processing with a high pass filter, implemented by the computer. The gain is further increased, and the QRS complexes are further magnified and distorted by the filters. They appear as rapid, multiple deflections while the terminal portions now more clearly show the late potentials. Thus, a high pass filter will distort a wave by removing some of its frequency components. Panel D depicts the final step in deriving the waveform most commonly used in the late potential analysis, the vector magnitude. This is formed from the filtered XYZ leads using the formula from analytic geometry $(X^2 + Y^2 + Z^2)^{½}$. This results in a single waveform which has only positive values. Two points are identified from this waveform. The first is the onset of the QRS duration, shown in panel D as a vertical line. The second identification point is the QRS offset, shown as a second vertical line. These two points form the basis for three derived parameters. The first is the QRS duration and is simply the difference of QRS offset and QRS onset (often referred to as fQRS duration or QRSd). The next two parameters rely primarily on the QRS offset point. The shaded region of the filtered vector magnitude depicts the last 40 ms of the QRS complex. The root mean square (RMS) voltage of this terminal 40 ms (V40 or RMS40) is calculated. The low amplitude signal (LAS) is the duration of the signal from a 40-microvolt voltage at the end of the QRS to the QRS offset point. The QRS duration is a measure of the total ventricular activation time. That is, it portrays the time from the earliest ventricular activation to the time of the latest ventricular activation. The V40 and LAS are waveform measures and do not directly relate to the electrophysiology of the heart as the QRS duration does. Essentially, a late potential appears as a low level "tail" after the main body of the QRS complex. The RMS and LAS are designed to be descriptors of this late potential tail.

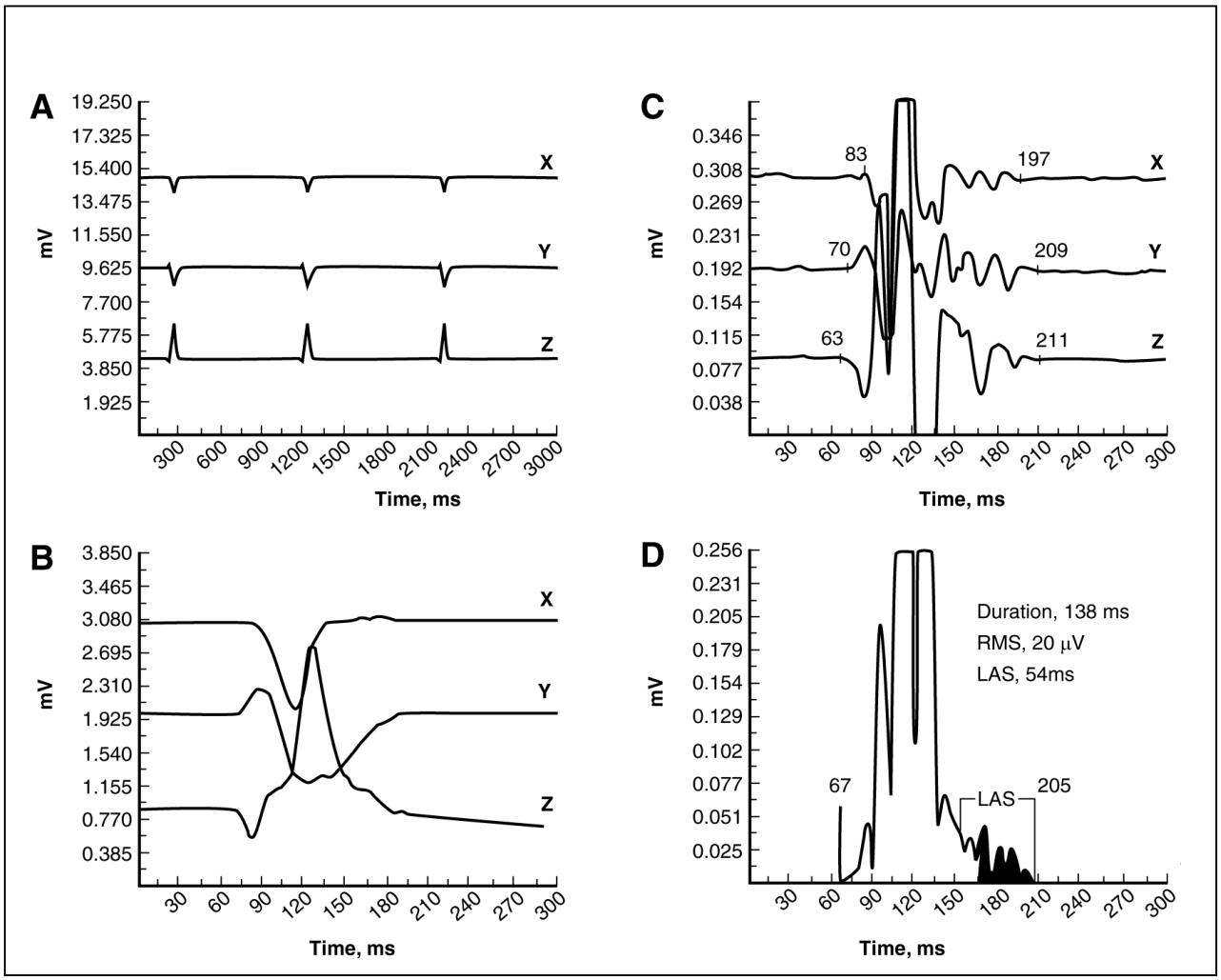


Figure 2—The process of signal-averaged ECG recording and analysis. See text for details.

7.2 Clinical application of the SAECG

7.2.1 Predischarge risk stratification after acute MI

Replacement with scar tissue of formerly healthy and functioning myocardial tissue is the hallmark of healed myocardial infarction (MI) and is reflected noninvasively in the left ventricular ejection fraction (LVEF). However, specific electrical and pathologic characteristics of the scar are closely tied to the expression of ventricular tachycardia (VT) and may explain the ability to use clinical tools in addition to ejection fraction (EF) to predict arrhythmia. The interruption of normal myocardial cell-to-cell coupling, anisotropic conduction, and irregularity of infarct border tissue may all contribute to myocardial conduction delay, an important determinant of reentrant VT (A.17). The degree of conduction delay in sinus rhythm can be assessed noninvasively with the SAECG. With this background, several investigators have prospectively identified patients after myocardial infarction, recorded the SAECG, and then followed these patients for the development of spontaneous sustained ventricular arrhythmias or sudden cardiac (and presumed arrhythmic) death. The studies differed somewhat in enrollment criteria and often in SAECG methodology but have been remarkably uniform in their conclusions.

In 1983, Breithardt et al. (A.18) published the first study that recognized the prognostic importance of the SAECG. Late potentials were visually identified as low amplitude activity at the end of the QRS, and when patients were

grouped by the absence of late potential or the presence of a short duration late potential (<20 ms), there was a lower incidence of sustained VT (0%) and sudden death (3.8%) than their counterparts with prolonged late potentials ($p<0.01$). Those patients with the longest late potentials (>40 ms) had a sudden death rate of 11% and VT rate of 17% in short-term followup. This first prospective study showed that late potentials could be detected after MI and, when present, could predict serious ventricular arrhythmias. This study also found that patients with inferior MI were more likely to have late potentials than patients with anterior MI, presumably because of the normal late activation of the posterior septum.

A number of later prospective studies began to utilize a quantitative approach to SAECG analysis, based on the work of Simson (A.19). Quantitative analysis lends itself to greater precision, can minimize investigator bias, and facilitates comparisons between and among investigative and clinical centers. The quantitative details used from study to study differed slightly and may account for differences in the incidence of SAECG abnormalities and, to a lesser extent, prediction of clinical endpoints.

In a study of 165 patients, Kuchar et al. (A.20) performed SAECG as well as Holter ECG and LVEF before hospital discharge. Patients were followed for at least 6 months. The SAECG revealed an abnormality in 41% of patients. Cardiac events classified as ventricular arrhythmias were observed in 8% of the study cohort and were much more common in the patients whose SAECG was abnormal. Survival without an arrhythmic event to 1 year was 99% in the patients with a normal SAECG but only 83% in the group with abnormal SAECG, a difference that was statistically significant. Although the SAECG had good sensitivity and moderate specificity, the positive predictive accuracy was only 17%. This was less than LVEF <40% but equal to Holter detected ventricular arrhythmia with positive predictive values of 23% and 17%, respectively.

The risk of an arrhythmic event was higher for the patients with abnormal SAECGs, but the majority of this subset did not experience an event in followup. To place these findings in context, it is important to emphasize that the predictive value in prospective studies is not only dependent on the intrinsic value of the designated test but also on the event rate in the population studied, which in turn depends upon the characteristics of the patients and the duration of followup (most arrhythmic events, however, tend to cluster in the first 3–6 months after MI).

7.2.2 Using the SAECG in combination with other noninvasive test results to predict serious ventricular arrhythmias after MI

In the early 1980s, it became firmly established that the LVEF and the frequency and complexity of ventricular arrhythmia on Holter ECG could predict the development of sustained ventricular arrhythmias after acute MI (A.21).

The relationship among noninvasive variables including the SAECG as prognostic tests after MI was explored in a study of 210 patients (A.22). These investigators hypothesized that the low specificity of the SAECG could be overcome by combining it with other test results. Only 15 patients experienced either sudden cardiac death or sustained VT. Three noninvasive tests provided results that were predictive of these arrhythmic events: an abnormal SAECG (odds ratio = 24), an LVEF < 40% (odds ratio = 18), and complex ventricular ectopy on Holter (odds ratio = 8). All three were independently predictive by multivariate analysis. The probability of an arrhythmic event was amplified when the tests were used in combination. The likelihood of an arrhythmic event was quite low in the 14-month followup of the study cohort when either the Holter or the SAECG was normal but markedly higher when both were positive. The event rate jumped from 6% or less to >30% in the subset with both Holter and SAECG abnormal. Similarly, the SAECG was analyzed with the LVEF. The risk of an arrhythmic event increased from 0–4% or less to 34% in patients with a LVEF <40% who had an abnormal SAECG. The specificity was improved when using the SAECG in combination with these other tests, to a level approaching 90%, without a major loss of sensitivity.

These observations suggest that the SAECG can help identify which patients with severe left ventricular dysfunction or ventricular arrhythmia have the conduction characteristics required to sustain fatal arrhythmic events. Conversely, extensive ventricular damage or the presence of arrhythmic triggers are generally needed to initiate and perpetuate these dangerous arrhythmias.

A detailed analysis of the interaction among left ventricular function, spontaneous ventricular arrhythmia on Holter ECG, and the signal-averaged ECG was also performed by Steinberg et al. (A.23). This prospective study enrolled 182 patients in the convalescent period after acute MI. The presence of an abnormal SAECG result was not strongly related to the presence of left ventricular dysfunction or spontaneous ventricular arrhythmia on Holter. The LVEF was depressed (<0.40) in 45% of patients with an abnormal SAECG compared to 38% in patients with well-preserved LVEF (p = NS). The presence of ventricular arrhythmia on Holter was found in 35% of patients with an abnormal SAECG result and 25% of patients with a normal SAECG (p = NS). Similar to findings of other contemporary studies (A.22, A.24-A.28), this investigation found that left ventricular function, Holter ECG detection of frequent or complex ventricular arrhythmia, and the SAECG findings were all significant predictors of arrhythmic events during followup.

Of the three SAECG variables typically measured, the fQRS provided the only independent contribution to risk prediction (A.23, A.29) rather than the RMS V40 or LAS.

Strategies for use of screening tests can be designed for two purposes: to identify or to exclude high risk. In this study (A.23), the individual screening tests performed suboptimally regardless of the desired purpose although the SAECG yielded the best sensitivity. Screening tests used in combination performed much better and at levels where meaningful clinical decisionmaking could result. For example, the absence of left ventricular dysfunction, Holter arrhythmia, and abnormal SAECG virtually excluded the development of dangerous ventricular arrhythmias after MI (negative predictive accuracy of 98%). The presence of both Holter arrhythmia and positive SAECG findings pinpointed a subgroup of post-MI patients (about 13% of total group) at extremely high risk. This subgroup had an event rate of 25% at 1 year and 60% at 2 years of followup, far greater than the remainder of the post-MI population. This level of risk clearly warrants grave concern, close followup and optimal post-MI therapy.

The independent prognostic value of the SAECG may be hampered by drawing conclusions from relatively small studies (and thus endpoints) performed at single institutions. If the SAECG is to be used as a screening test in clinical trials, as a surrogate endpoint in clinical investigation, and as a test guiding clinical practice, it must be shown with a high degree of confidence that the SAECG is providing unique clinical data in terms of risk stratification. Despite the logic and uniqueness of measuring ventricular conduction, it is not inconceivable that the data provided by the SAECG overlap with those provided by other readily available and well-established tests. From Figure 3, it can be seen that the SAECG results often did not provide risk data independent of these clinical tests if interpretations were restricted to the individual trials. In a meta-analysis of published trials that used these noninvasive screening tests to predict risk after MI, it was clearly established from the pooled results that the SAECG provided independent risk information (A.30). From three studies (A.22-A.24) that followed almost 500 patients, the SAECG predicted a sixfold increase in risk independent of LVEF. From four studies (A.22-A.25) that followed more than 650 patients, the SAECG predicted an eightfold increase in risk of arrhythmic events independent of ventricular arrhythmia on Holter ECG. A recent Cardiac Arrhythmia Suppression Trial (CAST) substudy of over 1000 patients (A.31) largely confirmed these relationships, although the results may have been biased by use of CAST antiarrhythmic drugs in some patients, selection of a low-risk patient population, and inconsistent performance of noninvasive screening tests at participating centers.

Finally, a recent prospective study of 416 patients (A.32) integrated a new noninvasive measure of sympatho-vagal autonomic balance, heart rate variability (HRV), with previous tests known to be predictive of postinfarction arrhythmic events. As opposed to the SAECG, HRV was significantly (but weakly) related to the LVEF and frequency of ventricular arrhythmia on Holter. Patients with reduced HRV were also more than twice as likely to have an abnormal SAECG: 37% vs 16%. In a mean followup approaching 2 years, there were 24 arrhythmic events. The HRV was markedly reduced and the presence of late potentials much higher in the patients who experienced an arrhythmic event. It was apparent that patients were far more likely to develop postinfarction arrhythmic events if any one of several noninvasive tests was abnormal but, most prominently, the HRV analysis and the SAECG. Interestingly these patient characteristics also predicted nonarrhythmic cardiac death. However, tests were associated with low positive predictive accuracy (<20%) and were evaluated in various combinations to improve risk stratification. The combination of an abnormal HRV and presence of a late potential was a particularly ominous finding; the risk of an arrhythmic event was increased 18-fold. Of all tested combinations, the presence of an abnormal HRV and late potential maintained a sensitivity >50%.

Table 1 summarizes the clinical use of combination noninvasive testing after MI.

7.2.3 Clinical limitations of the SAECG after MI

The aforementioned prospective studies grouped together all presumed "arrhythmic events," including patients who had sustained VT with those who had documented cardiac arrest due to VF and those who had sudden, often unwitnessed, death. Because the electrophysiologic substrate may differ between stable VT and unstable ventricular tachyarrhythmias (A.17), it may be more appropriate to examine SAECG variables based on more specific arrhythmic outcomes (A.33) in prospective studies. Unfortunately, the small number of arrhythmia-specific events in all published trials makes this analysis problematic. One group (A.34) has raised the possibility that important differences in SAECG variables may exist for the prediction of sustained VT relative to sudden death. Further work will be needed to fully address this concern.

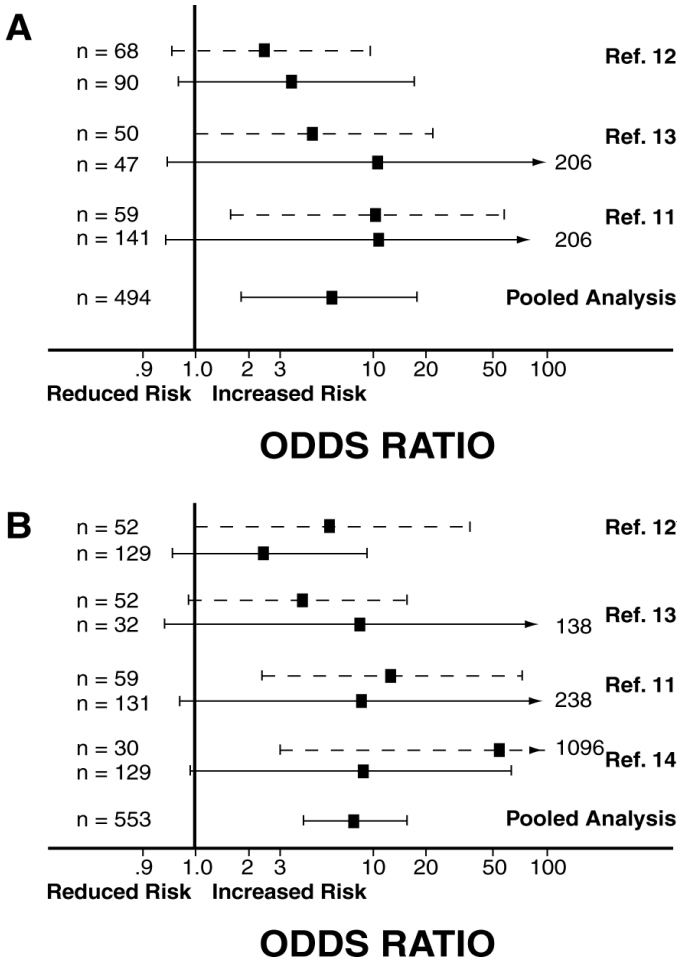


Figure 3—Odds ratios for risk of arrhythmic event after MI

A—Odds ratios for risk of arrhythmic event after myocardial infarction when signal-averaged ECG was abnormal with left ventricular ejection fraction dichotomized at 40% from three prospective studies. Dashed lines are left ventricular ejection fraction <40%, solid lines are left ventricular ejection fraction >40% and bold line is pooled results.

B—Odds ratios for risk of arrhythmic event after myocardial infarction when signal-averaged ECG was abnormal with Holter results dichotomized by presence/absence of significant ventricular arrhythmia from four prospective studies. Dashed lines are significant ventricular arrhythmia on Holter, solid lines are no significant ventricular arrhythmia on Holter and bold line is pooled results. Reprinted with permission. (A.23)

Table 1—Estimated value of the signal-averaged ECG combined with other noninvasive variables for predicting serious arrhythmic events after myocardial infarction

Variables	Risk of Event	
	For Normal Results (%)	For Abnormal Results (%)
SAECG and Holter	2	28
SAECG and EF	3	28
SAECG and HRV	7	33
EF and Holter	6	22
SAECG, Holter, EF	3	38
SAECG, Holter, HRV	4	43

EF = ejection fraction, HRV = heart rate variability, SAECG = signal-averaged electrocardiogram.

7.2.4 Interaction of invasive risk stratification with programmed ventricular stimulation and the SAECG

Programmed ventricular stimulation has been used to predict morbid or fatal arrhythmic events after MI. Like the SAECG, the induction of sustained monomorphic VT was thought to represent a specific indication of the presence of arrhythmic substrate for VT. However, the actual completion and perpetuation of the reentrant circuit was construed as a logical marker for the later clinical development of VT. This review will not attempt to fully discuss the merits and problems of this approach but will instead concentrate on the interrelationships between electrophysiologic study (EPS) and the SAECG. In concept, this interaction can take two forms: the SAECG can be used to predict which patients will have electrically inducible VT (as distinct from clinical or spontaneous VT) and thus screen for the EPS, or the SAECG can be used in conjunction with EPS if these results provide independent information.

In one of the most comprehensive studies of risk prediction after MI, Richards et al. (A.35) exposed 361 patients to a battery of tests, both invasive and noninvasive. Not all patients underwent all tests, but most patients underwent EPS, SAECG, nuclear radionuclide angiogram, 24-hour Holter ECG and exercise test. The SAECG was analyzed as an unfiltered 3-lead recording, and the duration of ventricular activation (earliest on any lead to latest on any lead) was prolonged if >120 ms. Terminal QRS measurements were not utilized. Patients were followed for more than 2 years and did not receive routine beta blocker therapy.

There were 34 deaths during followup, of which 8 were sudden, and there were 9 patients who survived episodes of sustained VT or ventricular fibrillation (VF). The risk of either sudden death or VT/VF was increased when patients had inducible VT at EPS (*relative risk* = 15), reduced LVEF (*relative risk* = 4.8) or abnormal SAECG (*relative risk* = 4.4). Other noninvasive tests did not contribute to risk prediction. With multivariate analysis, only inducible VT and LVEF made significant contributions, and the EPS was clearly the critical variable for any possible model. For cardiac death (including death due to arrhythmia, ischemia, and heart failure), the SAECG was the most powerful predictor (*relative risk* = 7), followed by EPS (*relative risk* = 5.6) and LVEF (*relative risk* = 5.2); all three were independent predictors as determined by multivariate analysis (A.35).

In an earlier study, these same investigators examined the overlap of results between SAECG and EPS (A.36). Interestingly, in this cohort these tests had similar predictive values, but the correspondence between tests was imperfect. Of the 80 patients with "delayed potentials," 11% had inducible VT. Although VT inducibility was uncommon even in this group, it was still far more frequent than in the much larger group without delayed potentials in whom VT was induced in only 4 of 226 patients or 2%. However, using the SAECG to screen for EPS would have missed 4 of the 13 patients with VT (30%), a substantial false negative finding. Because of this incomplete overlap between SAECG and EPS, more data will be needed to demonstrate that the noninvasive SAECG can predict with accuracy the invasive EPS results in this particular setting.

Employing a two-step screening strategy, Pedretti et al. (A.37) followed post-MI patients after discharge from a rehabilitation hospital. All patients underwent a series of noninvasive tests, including Holter, SAECG, and LVEF; "high risk" patients underwent EPS if at least two noninvasive variables were abnormal. In the high-risk subset (approximately 15% of the total group), about 40% had inducible sustained monomorphic VT. Those with inducible VT had an extremely high event rate, 65%, in followup. The allure of a strategy of noninvasive prescreening followed by invasive risk stratification rests on its logical premise and presumed clinical efficiency. Additional prospective investigation with more complete patient participation and antiarrhythmic drug-free followup is clearly needed.

Results of these studies indicate that EPS provides the most important information regarding arrhythmic risk stratification. However, EPS is not universally available, is expensive, and has a small risk. It clearly cannot be the procedure of choice unless and until the results of EPS are specifically needed for risk modification because of the need to focus on those at greatest risk or to learn the characteristics of the potential VT circuit.

Although the EPS is the single best predictor of spontaneous VT and sudden cardiac death, noninvasive risk prediction with SAECG, Holter, LVEF, and newer modalities such as HRV has clear-cut and important clinical relevance. The relevance of using an invasive strategy (or for that matter a noninvasive strategy) to guide the initiation of antiarrhythmic medical therapy is unproven at best and hazardous in some instances. Future studies must clarify the complementary role of noninvasive and invasive screening strategies as they specifically relate to outcome after treatment, not simply risk, before any recommendations can be made regarding risk modification.

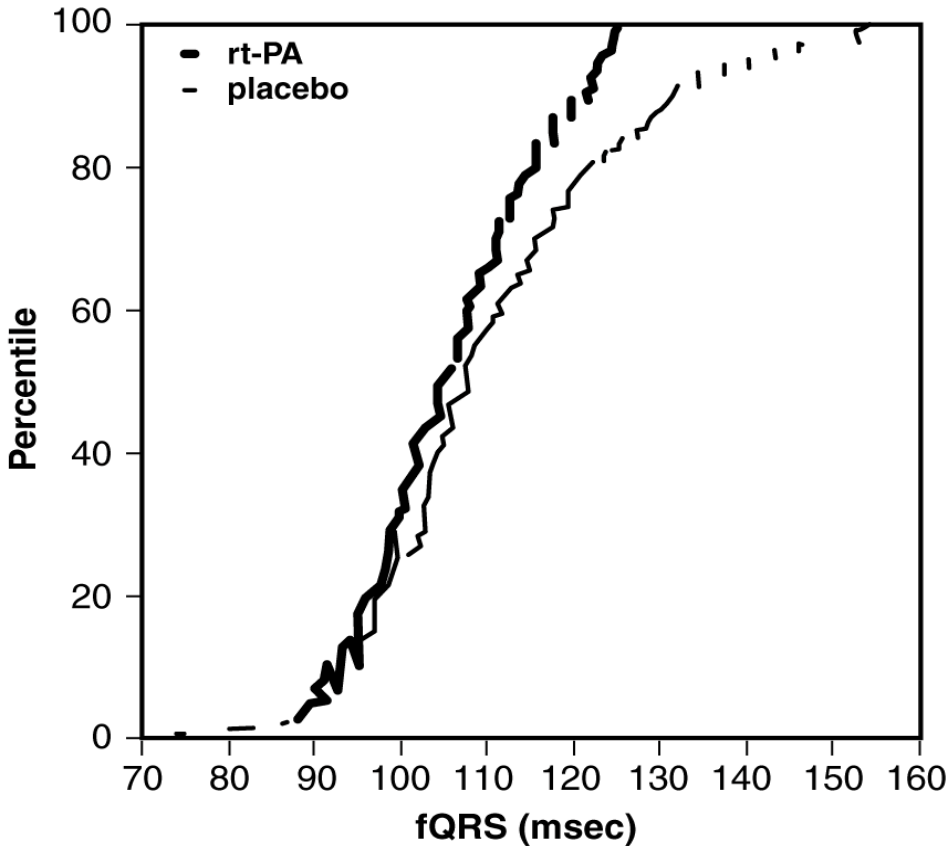


Figure 4—Plot of the proportional distribution of patients relative to filtered QRS (fQRS) duration according to treatment assignment in randomized trial of late thrombolytic therapy. There is consistent leftward shift in rt-PA-treated patients that becomes greater at longer fQRS values. More patients had less prolonged fQRS throughout the range of fQRS if treated with rt-PA. Reprinted with permission (A.42).

7.2.5 The clinical utility of the SAECG in the thrombolytic era

Attempts at reperfusion of occluded coronary arteries, most commonly with thrombolytic therapy, is now a standard treatment for acute MI and has reduced cardiac mortality. Most of the SAECG studies for stratifying post-MI risk were performed before the thrombolytic era, which raises several questions. Does thrombolytic therapy or the patency of the infarct artery alter the likelihood of developing an abnormal SAECG? Is the SAECG still of value in predicting arrhythmic risk when patients are routinely treated with thrombolytic therapy? Several recent efforts provide solid data relevant to these issues.

There have been several uncontrolled studies which observed a significant decrease in the frequency and severity of SAECG abnormalities in patients after thrombolysis (A.38-A.41) and even greater improvement (sometimes striking) in patients in whom the infarct artery was shown to be patent at subsequent angiography (A.38-A.41). However, despite the concordance of findings, these trials were regarded with caution because of the absence of prospective, randomized, or placebo-controlled series.

More recently, a prospective, randomized, and placebo-controlled study of the effect of thrombolysis on the SAECG was published a part of a multicenter investigation (A.42). The SAECG was improved when reperfusion therapy was administered as late as 6 to 24 hours after onset of symptoms. The fQRS was shortened, and the proportion of patients with a prolonged fQRS was reduced in the treated group of 150 patients compared to the placebo group of 160 patients. It is noteworthy that the improvement in SAECG was limited to patients who presented with ST elevation on their ECGs. In this group of 185 patients, the frequency of SAECG abnormality was halved. Moreover, there was a consistent leftward shift of the plot of fQRS duration to less pronounced prolongation throughout the range of measured values (Figure 4). In those without ST elevation, no improvement was seen. These observations

suggest that reperfusion of a totally occluded infarct artery, even relatively late after onset of symptoms of MI, leads to a more stable electrical substrate which likely reflects a meaningful, if not substantial, mechanism of mortality benefit.

Although the benefit of medical reperfusion on the SAECG is clear, the possible advantages of more delayed mechanical reperfusion are less settled. One small study (A.43) suggested that angioplasty of a previously occluded infarct artery can cause resolution of late potentials during short-term followup. A larger study (A.44) found no such benefit although another intriguing observation was made. When the occluded infarct artery was successfully opened, the absence of SAECG abnormality predicted improvement in wall motion in the infarct zone. If these initial observations are confirmed, the SAECG may thus be useful to indicate viability of infarct zone myocardium.

The ultimate expression of ventricular tachyarrhythmias after MI is a complex and dynamic process. Although conduction delay as measured by the SAECG is a determinant of arrhythmia formation, an appropriate balance between conduction delay and recovery of excitability must exist for reentry to occur. These electrical properties may in turn be modulated by infarct pathology, ischemia, left ventricular volume, and nervous system innervation. These processes are all potentially related to the presence, timing, and degree of reperfusion. One such interrelationship, that between late potential formation and ventricular dilation, was examined by Zaman et al. (A.45). In this study, early phase late potentials (first week post-MI) predicted the development of ventricular enlargement several weeks later. The authors hypothesized that early myocardial cell slippage is responsible for both early conduction delay and later ventricular dilation.

Table 2 summarizes some of the published experience with use of the SAECG for risk prediction after MI when substantial segments of the clinical population have received thrombolytic therapy. The study populations have not uniformly received thrombolytic therapy but instead were treated on clinical grounds or part of nonrandomized clinical trials. Because many patients remain ineligible or untreated with thrombolytic therapy in contemporary practice, these studies may still reasonably reflect current post-MI patients.

Table 2—Prognostic value of the post-MI SAECG in the thrombolytic era

Arrhythmic Events (total group)					Prognostic Value of (+) SAECG						
Reference	**Total #/ # Thrombolytic Rx**	**SAECG Day No.**	**No. of (+) SAECG**	**Duration of F/U (mos)**	**SCD**	**VT-S**	**Sens**	**Spec**	**(+)PV**	**(-)PV**	**RR***
29	174/106	26±10	41 (24%)	14±8	4	4	75	82	18	98	13.0
37	331/130	5-11	48 (15%)	20	12	13	48	88	25	95	6.9
38	301/205	14	61 (20%)	13	11	2	64	81	11	98	7.5
39	173/88	10-20	41 (24%)	12±5	7	2	56	78	12	97	4.4
40	787/363**	5-30	97 (12%)	10±3	31	2	90	61	21	98	13.0

* Uncorrected
** Includes angioplasty in same patients

F/U = followup; MI = myocarial infarction; PV = predictive value; RR = relative risk; Rx = therapy; SAECG = signal-averaged ECG; SCD = sudden cardiac death; Sens = sensitivity; Spec = specificity; VT-S = sustained VT

Several general observations are worthy of emphasis. Mortality after MI continues to fall, due to many factors including thrombolytic therapy. Arrhythmic events parallel this trend as exemplified in these studies; arrhythmic event rates are substantially less than those reported in the earlier studies of SAECG. Studies of other arrhythmic endpoints, such as inducible VT at EPS, also show similar trends (A.46). Because of a low event rate, risk stratification tests face a more difficult burden, and prospective studies become more difficult to interpret due to the broader confidence intervals that are inevitably present.

Multivariate analysis in the study with the largest number of patients treated with thrombolysis (A.47) revealed a potent independent association between SAECG findings and arrhythmic events. This study did not include coronary

angiographic data. When Hohnloser et al. (A.48) evaluated the independence of SAECG risk prediction, it was discovered that although the SAECG was a univariate predictor, it was not independent of the patency of infarct artery on the coronary angiogram.

Sustained coronary perfusion appears to be a critical factor in the development of late serious arrhythmias after MI. Specific electrical properties of the ventricular myocardium may be modulated by a number of processes that are directly or indirectly affected by timely reperfusion during acute MI and also by sustained perfusion in the chronic phase of MI healing. These interdependent myocardial factors include infarct pathology, integrity of the infarct border zone, left ventricular remodeling and volume, and sympathetic innervation. Ventricular conduction, assessed by the SAECG, has a strong relation to the patency of the infarct artery; in patients exposed to pharmacologic thrombolytic therapy, the incidence of late potentials has been low in patients with patent infarct artery, and several times more common when the infarct artery was occluded (A.38, A.39, A.49, A.50, A.51). Early timing of thrombolytic therapy may not be as critical as the ultimate development of patency and sustained and complete perfusion of the culprit coronary artery (A.49, A.50, A.42). The ability of thrombolytic therapy to accelerate the rate of and increase the proportion of patients with infarct artery patency explains a lower incidence of SAECG abnormalities as well as a lower risk of mortality (A.48); these two outcomes are likely interrelated. Large scale clinical trials will be needed to definitively explore this issue.

There is clearly an interaction between successful reperfusion, patency of the infarct artery, and the development of arrhythmic substrate exemplified by the SAECG. Among noninvasive tests, the SAECG retains its predictive power for arrhythmic events. The combined use of angiographic and noninvasive results will need additional study in much larger populations than have been published to date. However, cardiac catheterization is not yet routinely performed to assess artery patency. Unless it is, or there are accurate noninvasive assessments of infarct artery patency, physicians must still rely on data that are easily and regularly obtainable.

7.2.6 Prognostic value of the SAECG in patients with idiopathic dilated cardiomyopathy or with advanced heart failure

Idiopathic dilated cardiomyopathy (IDC) is a primary myocardial disease of uncertain etiology that is characterized by left ventricular or biventricular enlargement and impaired contractility (A.52). Ventricular arrhythmias are a common manifestation of IDC. From a review of published studies, it is apparent that 12% of patients with IDC die suddenly and that of all deaths, 28% can be classified as sudden (A.52). Patients with IDC may present with sustained monomorphic VT, polymorphic VT, or VF. The mechanisms involved are more diverse than in coronary heart disease and may include reentry as well as those due to triggered and abnormal automaticity. In addition, such factors as abnormal electrolytes, high circulating levels of catecholamines, myocardial stretch and decreased myocardial contractility all may play a role in the pathogenesis of these ventricular arrhythmias.

Disorders of ventricular conduction on the ECG are common in IDC. Bundle branch block (BBB), especially Left BBB, is very frequent and correlates with the severity of disease including the degree of interstitial fibrosis. Nonspecific IVCDs are also a common ECG finding. Because interstitial fibrosis is a component of the pathology of IDC, it can cause conduction abnormalities of the specialized conduction system (as seen on ECG) but also disordered ventricular myocardial activation (as seen on SAECG). The extent of myocardial fibrosis as detected by endomyocardial biopsy has correlated with the degree of abnormality of standard SAECG variables (A.53).

In order to assess the SAECG as a risk predictor, Mancini et al. (A.54) studied a group of 114 patients referred to their center for evaluation of heart failure or for cardiac transplantation; clearly this represents a highly selected subset of all heart failure patients. Detailed workup led to the diagnosis of nonischemic cardiomyopathy in all patients, half of whom were termed idiopathic. The other half had a variety of primary causes. Patients without bundle branch block had a control SAECG. All patients were followed for the development of death, sustained ventricular arrhythmias, or urgent need for cardiac transplantation. Some patients received antiarrhythmic medications, and a few had an implantable cardioverter defibrillator.

Survival curves were generated for the entire cohort divided into three subgroups: patients with a normal SAECG (n = 66), patients with an abnormal SAECG (n = 20), and patients with bundle branch block (n = 28). There were striking differences in event-free survival among these subgroups using several different composite and individual endpoints, but the group with an abnormal SAECG consistently fared worst. For example, survival at 1 year without VT or death was 95% for patients with a normal SAECG and 88% for patients with bundle branch block but only 39% for patients with an abnormal SAECG (Figure 5). This observation was highly significant statistically. In fact, the risk of any endpoint event in the presence of an abnormal SAECG was increased 17-fold relative to the other subgroups. Additional analyses eliminating patients on antiarrhythmic drugs or patients with a previous history of serious ventricular arrhythmias did not alter the findings. Univariate predictors of adverse outcomes included the SAECG, New York Heart Association (NYHA) classification, peak oxygen consumption, QRS duration >120 ms on standard

ECG, past history of VT, and sex. With multivariate analysis, only SAECG and NYHA classification predicted the endpoints.

These results strongly support the notion that similar electrophysiologic processes may be at work in patients with IDC and patients with CAD. Presumably the presence of myocardial fibrosis resulted in disorganized ventricular conduction and thus abnormalities on SAECG. The SAECG identified a small subset of patients with an alarmingly high rate of fatal or serious events. It appeared that the SAECG results reflected a primary abnormality rather than a measure of disease severity, because patients with abnormal SAECG were comparable to patients with normal SAECG in a variety of variables reflecting ventricular performance. One cautionary note regarding this study is that the incidence of sudden death and sustained VT was low, possibly reflecting the benefits of contemporary therapy of heart failure patients. Survival analysis was performed on composite endpoints rather than specific arrhythmic endpoints, and relative risks of individual factors undoubtedly had broad confidence intervals. However, alone among many variables tested over many years, the SAECG was able to predict VT and death. Moreover, a normal SAECG, a surprisingly common finding, portended an excellent outcome. Whether the SAECG will be an important tool for the selection of specific antiarrhythmic treatment (e.g., amiodarone, implantable defibrillator) must await future clinical trials.

Mancini et al. also suggested that the SAECG may represent a promising technique for risk stratification in cardiac transplant candidates, especially given the acute shortage of donor hearts. However, in patients accepted for transplantation, two studies have found that no single SAECG variable, or combination, predicted mortality (A.55, A.56).

Patients with severe heart failure are frequently prone to alterations in hemodynamic parameters, especially to fluctuations in ventricular filling pressure. Acute and/or marked changes in ventricular filling pressures could potentially intensify coronary ischemia and adrenergic tone. In addition, the ventricular action potential is sensitive to changes in ventricular filling. Changes in the SAECG during heart failure decompensation would provide mechanistic information and also provide improved guidelines for use of the SAECG. However, a comprehensive analysis of the SAECG during aggressive therapy of CHF showed no major changes indicating a stable conduction substrate regardless of hemodynamic status (A.57).

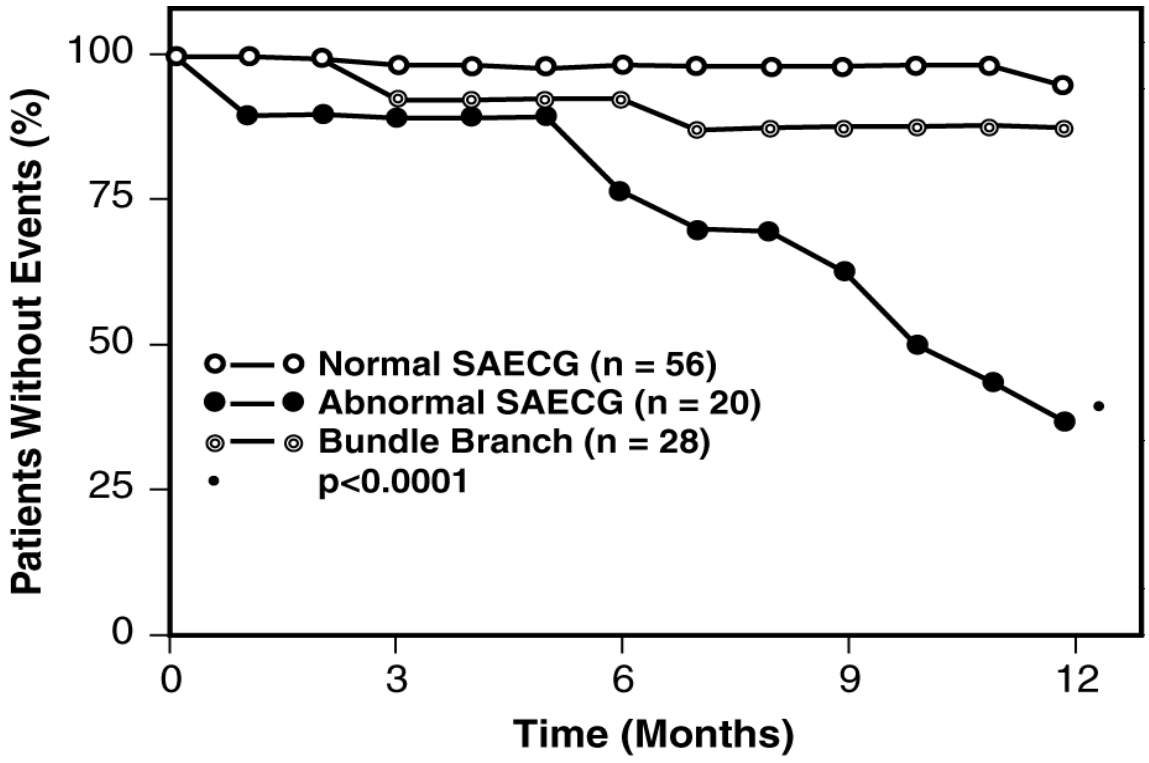


Figure 5—Survival curves displaying freedom from death or sustained ventricular arrhythmia in heart failure patients with normal or abnormal signal-averaged (SA) ECG and bundle branch block. Events were more frequent in patients with abnormal SAECG (p<0.0001). Reprinted with permission (A.54).

7.2.7 Predicting electrically induced ventricular tachycardia in the electrophysiology laboratory of patients with unexplained syncope

In patients with unexplained syncope, the electrophysiologic study is used to provide information supportive of a variety of bradyarrhythmic and tachyarrhythmic cardiac diagnoses, and provides relevant information in at least half of cases. In anywhere from 15-35% of cases, sustained VT is diagnosed as the cause of syncope. This diagnosis is particularly important because undiagnosed syncopal VT may recur and may be fatal. Untreated VT carries a substantial risk and successful suppression or treatment presumably reduces the risk of VT recurrence and sudden death.

A large prospective study highlighted the SAECG (A.58). A variety of causes were found by prolonged ECG monitoring and by EPS in 150 patients with undiagnosed syncope. EPS was only performed in a select subset and VT was diagnosed in 22 subjects but was sustained in only 12 (spontaneous VT in 4 and induced VT in 8). For the diagnosis of VT, the SAECG had a sensitivity of 73%, a specificity of 89%, and a predictive accuracy of 54%. These investigators also highlighted the importance of the combination of heart disease and the SAECG; the presence of coronary artery disease and an abnormal SAECG had a predictive accuracy of 82%.

Holter ECG recording is almost always performed as part of the workup for the syncopal patient. Winters et al. (A.59) examined the SAECG as well as the quantity of ventricular arrhythmia on the Holter recording in 40 patients with undiagnosed syncope. Neither the frequency of ventricular premature beats nor the presence of nonsustained VT was related to the presence of inducible VT. In contradistinction, the SAECG variables distinguished patients with inducible VT from those without VT. The sensitivity of individual SAECG variables ranged from 50–83% and the specificity from 82–91%, with the strongest association between VT and the RMS V40 results.

These studies suggested that the SAECG may be useful as a screening test for VT in patients who have unexplained syncope, but interpretation was hampered by small sample size, use of spontaneous nonsustained VT as an endpoint, and failure to perform programmed stimulation with three extra stimuli to maximize sensitivity of EPS. Most recently, a multicenter group of investigators collected prospective data on a large number of patients with at least one episode of unexplained syncope or severe near-syncope who were referred to the respective institutions (A.60). There were 189 patients enrolled, of whom about one quarter had either prior MI or nonischemic left ventricular dysfunction; about one third had no identifiable heart disease. All patients underwent EPS, and sustained monomorphic VT was induced in 28 patients or 15% of the total group; a detailed analysis of potential predictors of inducible VT was undertaken.

Patients with VT were neither older nor characterized by sex. However, one piece of historical data was different: more than three times more patients with VT had a history of prior MI than patients without VT. As previously suggested, the results of Holter recording had no correlation with VT inducibility. All SAECG variables were associated with VT, although the most striking differences were observed with the fQRS determination. Of the group with VT, 70% had a fQRS prolonged >110 ms compared to only 45% of those without VT ($p = 0.02$).

Using the SAECG with other clinical variables affected the predictive value. As shown in Figure 6, a receiver operator curve was constructed using three variables (prior MI, EF < 0.40, and SAECG) alone and in various combinations. The SAECG had the highest sensitivity but poor specificity. Although history of prior MI or a low EF was a more specific finding, the sensitivity of each was low. Combining variables improved sensitivity, specificity, or both. The combination of prior MI and abnormal SAECG had an excellent specificity. In addition, this combination yielded a high positive predictive value: 60% of these patients had inducible VT. The absence of history of MI, low EF, or SAECG abnormality had excellent sensitivity and a low risk of VT (negative predictive value of 93%).

With multivariate analysis, only two variables were identified as independent: a history of prior MI and the SAECG results. The risk of inducible VT was increased 3- to 5-fold if either was present and 17-fold if both were present. The SAECG thus identified a unique feature of the patients' clinical profile, myocardial conduction delay in the absence of bundle branch block.

Using logistic regression techniques, a model was created based on the use of sequentially performed tests in order to determine the incremental predictive value of noninvasive screening for inducible VT in patients with unexplained syncope (A.54). Based on the patient's history, in essence the presence of prior MI, two groups were formed: a low-risk group (no MI) with a probability range for VT of 5–13% and a moderate-risk group (prior MI) with a probability range for VT of 28–42%. History alone could not assign risk above 50%.

The SAECG, when added to the history model, added significant incremental information to the total group, assigning high likelihood (>50%) to most VT patients. When performed after SAECG, other noninvasive tests did not increment

the predictive value any further. Of the moderate-risk group (history of MI), the SAECG was able to stratify risk — the risk was twice as high when the SAECG was abnormal. Thus, the SAECG performed well with these "gray zone" patients.

Interestingly, the SAECG had no incremental predictive value when used in the low-risk group. The presence of an abnormal SAECG without MI (such as in patients with IDC, or in the absence of heart disease) meant it was likely a false positive result. The low-risk group presented a particular screening problem as it represented about 80% of the patients. Only the combination of an abnormal SAECG using the most stringent definition (fQRS >120 ms and all three criteria abnormal) and a Holter revealing frequent or complex ventricular arrhythmia significantly predicted greater risk of inducible VT. Patients without prior MI may be particularly problematic because of problems inherent in the screening tests or in the EPS itself.

The SAECG has a prominent role to play as a predictor of inducible VT in patients with unexplained syncope. The laboratory induction of VT has important implications for treatment. Further prospective study will be needed to answer whether the SAECG predicts spontaneous VT or sudden death in these patients.

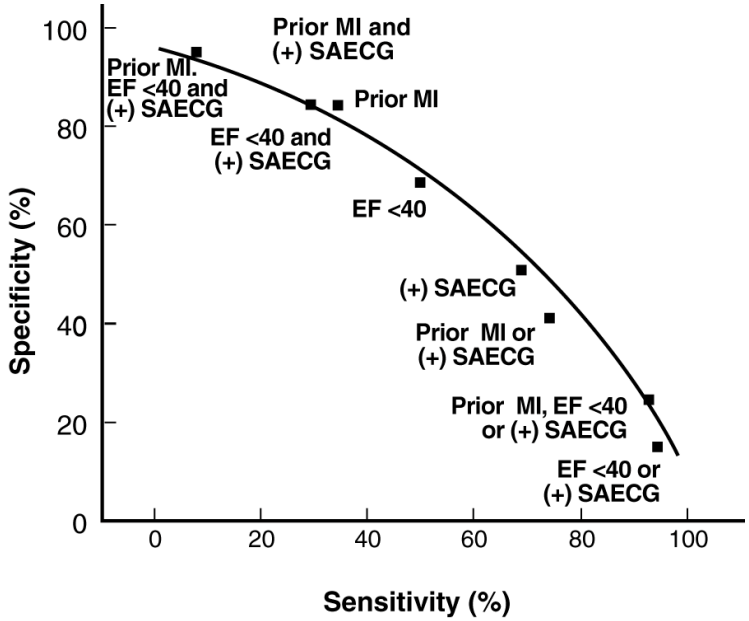


Figure 6—Prediction of inducible ventricular tachycardia in patients with unexplained syncope, based on presence of single or combination noninvasive variables. EF = ejection fraction, MI = myocardial infarction, SAECG = signal-averaged ECG. Reprinted with permission (A.60).

7.2.8 Predicting inducibility of sustained VT in patients with nonsustained VT

The detection of nonsustained VT (NSVT) on ECG, telemetry recording, or Holter ECG is associated with adverse outcome. This association, limited to those with ventricular dysfunction, appears to be present whether the NSVT is recorded in the convalescent phase of an acute event (e.g., MI) or during the chronic followup of patients with significant left ventricular (LV) dysfunction. Although NSVT is viewed with grave concern, the management of these patients is as yet uncertain. Several multicenter trials are under way, and their results should largely clarify the appropriate strategy to employ in these patients.

If EPS is the selected approach to management of the patient with NSVT, it is unclear if all patients need be studied or if it is more efficient, clinically prudent, and cost effective to perform EPS on prescreened subgroups. Several studies have examined the relationship of a variety of clinical and noninvasive variables to inducibility of VT, and none save EF and SAECG has proven useful.

Several studies have examined the use of the SAECG to predict inducible VT in patients with NSVT (A.61–A.63). In the largest study, 105 heterogenous patients with NSVT were studied (A.63). The study population included a large

number of subjects with prolonged symptoms such as syncope which may have represented an episode of undiagnosed spontaneous sustained VT and thus overestimated the incidence of sustained VT in this population. The analysis revealed that those patients with inducible sustained monomorphic VT (21% of the total group), were characterized by a history of syncope, a lower EF, and the presence of an abnormal SAECG. The differences in the SAECG results across patient groups were rather striking. For example, the fQRS duration was more than 20 ms longer in the sustained VT group, and late potentials were identified at least three times more commonly than in the groups with either inducible VF or no inducible arrhythmia. The sensitivity of the SAECG for inducible VT ranged between 64% and 73%, and the specificity between 71% and 89%, depending on SAECG definition (A.63). One study (A.61) had raised concerns about the inability to predict sustained VT in patients with anterior MI. Interestingly, this larger study (A.63) demonstrated that the SAECG was as likely to be abnormal in the patients with CAD (25%) as in those with IDC (23%). Furthermore, the predictive accuracy was similar in these two groups (A.63). In a multivariate analysis, SAECG had the strongest association with inducible VT. However, the results of EPS and SAECG were not completely concordant; the SAECG misidentified 16% of the patients, based on EPS results.

Although the total number of patients studied has not been overwhelming, there is a consistency of results in patients after MI with NSVT (A.61–A.63); the results of programmed ventricular stimulation can be predicted by the SAECG with good although imperfect accuracy. Because about three quarters of these patients will not have inducible VT, there are great advantages to screening out those with a low risk of having a positive EPS result. The SAECG is typically advantageous in this regard due to its high negative predictive accuracy. Effective screening would result in major cost savings by avoiding EPS in a sizable proportion of the total at-risk population. Based on the observations of the published studies, the inducibility rate of VT is approximately 25%; the negative predictive accuracy of the SAECG for this endpoint is approximately 90%. In a hypothetical group of 100 patients with ischemic heart disease and NSVT, one could expect to correctly screen out 54 patients, miss EPS inducibility in only two or three patients, identify EPS inducibility correctly in 22 patients, and perform EPS in 21 noninducible patients. It is unknown whether the EPS or the SAECG provides stronger prognostic data and thus how patients with discordant SAECG and EPS results should be risk stratified.

The aforementioned approach presupposes that the EPS is the optimal test to predict arrhythmic outcome and that it provides patient-specific data that can be used to guide drug or device therapy. An alternative strategy could be based on a noninvasive approach to maximal risk stratification followed by long-term antiarrhythmic therapy. This method could avoid more costly testing and treatment interventions. Amiodarone is being evaluated in several ongoing treatment trials, although none specifically target patients with MI, left ventricular dysfunction, NSVT, and abnormal SAECG.

8 Emerging areas in signal-averaged ECG

8.1 Frequency domain analysis

Although time domain late potential analysis has proven useful in many clinical settings, there are a few limitations that have been recognized. These include occasional inability to distinguish noise from late potentials and inconsistent definitions of cut-off values for time domain parameters in borderline results. More crucial is the difficulty in diagnosing patients with bundle branch block and other types of intraventricular conduction delays. This is because conduction delays tend to extend the high amplitude portion of the QRS vector magnitude into the late potential region, thereby resulting in either a false positive or false negative. Therefore, an alternative assessment of the SAECG data is warranted.

Frequency domain analysis has been proposed as such an alternative (A.64–A.83). The signals generated by the myocardium during systole comprise numerous signal components of different cycle lengths (frequencies) and amplitude. Frequency analysis considers these unique contributions of the “frequency” components, whereas time domain assesses changes in voltage with respect to time. New signal processing techniques for SAECG analysis are still evolving, including frequency domain (spectral) analysis (A.65, A.75, A.77, A.78), joint time-frequency (spectro-temporal) analysis (A.68, A.69, A.83), and wavelet analysis (A.82). These new mathematical analysis techniques may have a potential role in the field of noninvasive electrocardiology.

8.2 P-wave signal-averaging and analysis methods

Another application of signal-averaging methods is P-wave signal averaging (P-SAECG) during sinus rhythm. For P-SAECG analysis, the ECG data (X-, Y-, Z-lead ECG data amplified and digitized at 1000 samples per second and 16 bits per sample) similar to that used in the QRS (ventricular late potential) analysis is acquired and analyzed. High-resolution, low-noise P-wave signals are obtained by correlation of the P waves with a P-wave template formed at the beginning of the averaging and aligning process. The averaged P-wave signals are high pass filtered, and a vector magnitude is computed from the filtered X, Y, Z lead signals as in the QRS analysis. P-wave onset and offset

are determined using thresholds based on the measured noise levels.

Atrial fibrillation is a potential risk for systemic thromboembolisms and other cardiovascular risks. P-SAECG is being evaluated as an important noninvasive method for identifying patients at risk for paroxysmal atrial flutter and also to identify patients who are at risk to develop chronic atrial fibrillation (A.84–A.90). Some of these published studies have found that the most significant independent parameter derived from the P-SAECG study is the total filtered P-wave duration. However, a few of these studies have found that the RMS voltage in the terminal filtered P wave is also clinically useful.

8.3 Application of P-SAECG to measurement of atrial activation

Recent work has supported the concept that atrial fibrillation (AF) occurs on the basis of multiple reentrant circuits and as such will depend upon electrophysiologic conditions that promote and support reentry. Because reduced conduction velocity will facilitate the development of atrial reentry (i.e., AF) and because fixed activation abnormalities may exist even prior to AF, the SAECG has been used to measure total atrial activation times and to predict AF.

In a recent report by Guidera and Steinberg (A.91), the standard ECG was incapable of discriminating between patients with and without prior AF, but the P-SAECG showed substantial differences. Individual orthogonal leads, averaged and filtered, had P-wave durations that were approximately 25–30 ms more prolonged in the AF patients than in the matched controls, a difference of about 15%. The vector magnitude lead composite was also markedly more prolonged and facilitated good separation of P-wave values between the two groups. These results are similar to those reported by Fukunami et al. (A.92) and Stafford et al. (A.93), who studied patients with paroxysmal AF using different P-SAECG methodologies. Interestingly, left atrial dimensions did not differ between patients with and without AF despite the differences in P-wave characteristics.

In a prospective study of AF occurring after cardiac surgery, the clinical role of P-wave SAECG and the importance of preexisting atrial conduction abnormality to the development of AF was recently demonstrated (A.94). Two factors were found to predict AF in this setting: preoperative left ventricular ejection fraction and the P-wave duration on the preoperative P-SAECG. The P-SAECG provided the most accurate measure of risk with a sensitivity of 77% and a positive predictive accuracy of 37% for a P-wave duration >140 ms. The likelihood of developing AF was increased almost fourfold if the P-wave duration on preoperative P-SAECG was prolonged, independent of other clinical variables, indicating a preexisting propensity to AF that was triggered by cardiac surgery.

Annex A
(informative)

Cited references

A.1 BERBARI EJ, LAZZARA R, EL-SHERIF N, and SCHERLAG BJ. Extracardiac recordings of His-Purkinje activity during conduction disorders and junctional rhythms. *Circulation* 51(5):802–810, May 1975.

A.2 LIPPENS F, SAVARD P, and SHENASA M. Performance degradation of the coherent averaging technique by a molding effect. *IEEE Trans. Biomed. Eng*. 36:856-858, 1989.

A.3 REDDY BRS, CHRISTENSON DW, ROWLANDSON GI.,and HAMMILL SC. High Resolution ECG, *Medical Electronics* 23:60-73, 1992.

A.4 ROMPELMAN O, and ROS HH. Coherent averaging technique: A tutorial review. Part 2: Trigger jitter. overlapping responses and non-periodic stimulation. *J. Biomed. Eng*. 8:30-35, 1986.

A.5 LANDER P, BERBARI EJ, RAJAGOPALAN CV, VATTEROTT P, and LAZZARA R. Critical analysis of the signal-averaged electrocardiogram: Improved identification of late potentials. *Circulation* 87:105-117, 1993.

A.6 GOMES JA, WINTER SL, STEWART D, ET AL. Optimal bandpass filters for time-domain analysis of the signal-averaged electrocardiogram. *Am. J. Cardiol*. 60:1290-1298, 1987.

A.7 SIMSON MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. *Circulation* 64:234-242, 1981.

A.8 LANDER P, and BERBARI EJ. Use of highpass filters to detect late potentials in the signal-averaged ECG. *J. Electrocardiol*. 22(S):7-12, 1989.

A.9 SALTZSTEIN W, MEHTA N, and FLOWERS NC. A comparison of late potential variables using three commercially available signal averaging ECG Systems. *J. Am. Coll. Cardiology* 19 (3 Suppl. A):125A, 1992.

A.10 CHRISTENSON DW, REDDY BRS, and ROWLANDSON GI. Evaluation of Fourier transform filter for high-resolution ECG. *J Electrocardio.* 22(S):33-40, 1989.

A.11 HAMMILL SC, TCHOU PJ, KIENZLE MG, HAISTY WK, OZAWA Y, and UNDERWOOD DA. Establishment of Signal-averaged ECG criteria with Frank XYZ leads and spectral filter used alone and combined with ejection fraction to predict inducible ventricular tachycardia. *Amer. J. Cardiol.* 70:316-320, 1992.

A.12 MCCLELLAN JH, PARKS TW, and RABINER LR. A computer program for designing optimum FIR linear phase digital filters. *IEEE Trans. Audio Electroacoust*. 21:506-526, 1973.

A.13 LANDER P, and BERBARI EJ. Principles and signal processing techniques of the high-resolution electrocardiogram. *Pro-. Cardiovasc. Dis*. 35:169-187, 1992.

A.14 PIETERSON AH, GYMOESE E, and BREITHARDT G. Importance of the noise level for detection of late potentials in the signal-averaged electrocardiogram. *Circulation* 82:111-739, 1990.

A.15 BERBARI EJ, RAJAGOPALAN CV, LANDER P, and LAZZARA R. Changes in late potential measurements as a function of decreasing bandwidth. *J. Cardiovasc. Electro*. 2:503–508, 1991.

A.16 STEINBERG JS, and BIGGER JT JR. Importance of the endpoint of noise reduction in analysis of the signal-averaged electrocardiogram. *Am. J. Cardiol*. 63:556–560, 1989.

A.17 DENNISS AR, RICHARDS DA, WAYWOOD JA, ET AL. Electrophysiological and anatomical differences between canine hearts with inducible ventricular tachycardia and fibrillation associated with chronic myocardial infarction. *Circ. Res*. 64:155–166, 1989.

A.18 BREITHARDT J, SCHWARZMAIER M, BORGGREFE K, ET AL. Prognostic significance of late ventricular potentials after acute myocardial infarction. *Eur. Heart J*. 4:487–495, 1983.

A.19 SIMSON MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. *Circulation* 64: 235–242, 1981.

A.20 KUCHAR DL, THORBURN CW, and SAMMEL NL. Late potentials detected after myocardial infarction: natural history and prognostic significance. *Circulation* 74:1280–1289, 1986.

A.21 BIGGER JT JR, and STEINBERG JS. Risk stratification for arrhythmic death after myocardial infarction. In El-Sherif N, Samet P, eds:*Cardiac Pacing and Electrophysiology*. WB Saunders: Philadelphia, 1991, p.303.

A.22 KUCHAR DL, THORBURN CW, and SAMMEL NL. Prediction of serious arrhythmic events after myocardial infarction; signal-averaged electrocardiogram, Holter monitoring and radionuclide ventriculography. *J. Am. Coll. Cardiol.* 9:531–538, 1987.

A.23 STEINBERG JS, REGAN A, SCIACCA, RR, ET AL. Predicting arrhythmic events after acute myocardial infarction using the signal-averaged electrocardiogram. *Am. J. Cardiol*. 69:13–21, 1992.

A.24 GOMES JA, WINTERS SL, STEWART D, ET AL. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction; based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. *J. Am. Coll. Cardio.* 10:349–357, 1987.

A.25 CRIPPS T, BENNETT ED, CAMM AJ, ET AL. High gain signal-averaged electrocardiogram combined with 24 hour monitoring in patients early after myocardial infarction for bedside prediction of arrhythmic events. *Br. Heart J*. 60:181–187, 1988.

A.26 VERZONI A, ROMANO S, POZZONI L, ET AL. Prognostic significance and evolution of late ventricular potentials in the first year after myocardial infarction; a prospective study. *PACE* 12:41–51, 1989.

A.27 EL-SHERIF N, URSELL S, BEKHEIT S, ET AL. Prognostic significance of the signal-averaged ECG depends on the time of recording in the postinfarction period. *Am. Heart J.* 118:256–264, 1989.

A.28 RODRIGUEZ L, KRIJNE R, VAN DEN DOOL A, ET AL. Time course and prognostic significance of serial signal-averaged electrocardiograms after a first acute myocardial infarction. *Am. J. Cardiol*. 66:1199–1202, 1990.

A.29 GOMES JA, WINTERS SL, MARTINSON M, ET AL. The prognostic significance of quantitative signal-averaged variables relative to clinical variables, site of myocardial infarction, ejection fraction and ventricular premature beats: a prospective study. *J. Am. Coll. Cardiol*. 13:377–84, 1989.

A.30 YAKUBO S, OZAWA Y, TANIGAWA N, and YASUGI T. Detection of late potentials : Comparison of two commercial high-resolution ECG systems. *J Electrocardiol.* 25(suppl.): 151-155, 1992.

A.31 EL-SHERIF N, DENES P, KATZ R, ET AL. Definition of the best prediction criteria of the time domain signal-averaged electrocardiogram for serious arrhythmic events in the postinfarction period. *J. Am. Coll. Cardiol*. 25:908–914, 1995.

A.32 FARRELL TG, BASHIR Y, CRIPPS T, ET AL. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J. Am. Coll. Cardiol*. 18:687–697, 1991.

A.33 FREEDMAN RA, GILLIS AM, KEREN A, ET AL. Signal-averaged electrocardiographic late potentials in patients with ventricular fibrillation or ventricular tachycardia: correlation with clinical arrhythmia and electrophysiologic study. *Am. J. Cardiol*. 55:1350–1353, 1985.

A.34 ODEMUYIWA O, MALIK M, POLONIECKI J, ET AL. Differences between predictive characteristics of signal-averaged electrocardiographic variables for postinfarction sudden death and ventricular tachycardia. *Am. J. Cardiol*. 69:1186–1192, 1992.

A.35 RICHARDS DA, BYTH K, ROSS, DL, UTHER JB, ET AL. What is the best predictor of spontaneous ventricular tachycardia and sudden death after myocardial infarction. *Circulation* 83:756–763, 1991.

A.36 DENNISS AR, RICHARDS DA, CODY DV, ET AL. Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal-averaged electrocardiograms of survivors of acute myocardial infarction. *Circulation* 74:731–745, 1986.

A.37 PEDRETTI R, ETRO M, LAPERTA A, ET AL. Prediction of late arrhythmic events after acute myocardial infarction from combined use of noninvasive prognostic variables and inducibility of sustained monomorphic ventricular tachycardia. *Am. J. Cardiol*. 71:1131–1141, 1993.

A.38 GANG ES, LEW AS, HONG M, ET AL. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. *N. Engl. J. Med*. 321:712–716, 1989.

A.39 VATTEROTT PJ, HAMMILL SC, BAILEY KR, ET AL. Late potentials on signal-averaged electrocardiograms and patency of the infarct-related artery in survivors of acute myocardial infarction. *J. Am. Coll. Cardiol*. 17:330–337, 1991.

A.40 ZIMMERMAN M, ADAMEC R, CIARONI S, ET AL. Reduction in the frequency of ventricular late potentials after acute myocardial infarction by early thrombolytic therapy. *Am. J. Cardiol*. 67:697–703, 1991.

A.41 PEDRETTI R, LAPORTA A, ETRO MD, ET AL. Influence of thrombolysis on signal-averaged electrocardiogram and late arrhythmic events after acute myocardial infarction. *Am. J. Cardiol*. 69:866–872, 1992.

A.42 STEINBERG JS, HOCHMAN JS, MORGAN CD, ET AL. Effects of thrombolytic therapy administered 6 to 24 hours after myocardial infarction on the signal-averaged ECG. Results of a Multicenter randomized trial. *Circulation* 90:746–752, 1994.

A.43 BOEHRER JD, GLAMANN DB, LANGE RA, ET AL. Effect of coronary angioplasty on late potentials one to two weeks after acute myocardial infarction. *Am. J. Cardiol*. 70:1515–1519, 1992.

A.44 RAGOSTA M, SABIA PJ, KAUL S, ET AL. Effects of late (1 to 30 days) reperfusion after acute myocardial infarction on the signal-averaged electrocardiogram. *Am. J. Cardiol*. 71:19–23, 1993.

A.45 ZAMAN AG, MORRIS JL, SMYLLIE JH, ET AL. Late potentials and ventricular enlargement after myocardial infarction. *Circulation* 88:905–914, 1993.

A.46 SAGER PT, PERLMUTTER RA, ROSENFELD LE, ET AL. Electrophysiologic effects of thrombolytic therapy in patients with a transmural anterior myocardial infarction complicated by left ventricular aneurysm formation. *J. Am. Coll. Cardiol*. 12:19–24, 1988.

A.47 DENES P, EL-SHERIF N, KATZ R, ET AL. Prognostic significance of signal-averaged electrocardiogram after thrombolytic therapy and/or angioplasty during acute myocardial infarction (CAST substudy). *Am. J. Cardiol*. 74:216–220, 1994.

A.48 HOHNLOSER SH, FRANCK P, KLINGENHEBEN T, ET AL. Open infarct artery, late potentials, and other prognostic factors in patients after acute myocardial infarction in the thrombolytic era. *Circulation* 90:1747–1756, 1994.

A.49 AGUIRRE FV, KERN MJ, HSIA J, ET AL. Importance of myocardial infarct artery patency on the prevalence of ventricular arrhythmia and late potentials after thrombolysis in acute myocardial infarction. *Am. J. Cardiol*. 68:1410–1416, 1991.

A.50 LANGE RA, CIGARROA RG, WELLS PJ, ET AL. Influence of anterograde flow in the infarct artery on the incidence of late potentials after acute myocardial infarction. *Am. J. Cardiol*. 65:554–558, 1990.

A.51 MCCLEMENTS BM, and ADGEY AA. Value of signal-averaged electrocardiography, radionuclide ventriculography, Holter monitoring and clinical variables for prediction of arrhythmic events in survivors of acute myocardial infarction in the thrombolytic era. *J. Am. Coll. Cardiol*. 21:1419–27, 1993.

A.52 DEC GW, and FUSTER V. Idiopathic dilated cardiomyopathy. *N. Engl. J. Med*. 331:1564–1575, 1994.

A.53 YAMADA T, FUKUNAMI M, OHMORI MD, ET AL. New approach to the estimation of the extent of myocardial fibrosis in patients with dilated cardiomyopathy: use of signal-averaged electrocardiography. *Am. Heart J*. 126:626–631, 1993.

A.54 MANCINI DM, WONG KL, and SIMSON MB. Prognostic value of an abnormal signal-averaged electrocardiogram in patients with nonischemic congestive cardiomyopathy. *Circulation* 87:1083–1092, 1993.

A.55 MIDDLEKAUFF HR, STEVENSON WG, WOO MA, ET AL. Comparison of frequency of late potentials in idiopathic dilated cardiomyopathy and ischemic cardiomyopathy with advanced congestive heart failure and their usefulness in predicting sudden death. *Am. J. Cardiol*. 66:1113–1117, 1990.

A.56 PINSKY DJ, SCIACCA R, and STEINBERG JS. QT dispersion measured at the time of wait-listing is a powerful predictor of who will die awaiting heart transplantation. *J. Am. Coll. Cardiol*. 25:142 (abstract), 1994.

A.57 STEVENSON WG, WOO MA, MOSER DK, ET AL. Late potentials are unaltered by ventricular filling pressure reduction in heart failure. *Am. Heart J*. 122:473–477, 1991.

A.58 KUCHAR DL, THORBURN CW, and SAMMEL NL. Signal-averaged electrocardiogram for evaluation of recurrent syncope. *Am. J. Cardiol*. 58:949–953, 1986.

A.59 WINTERS SL, STEWART D, and GOMES JA. Signal-averaging of the surface QRS complex predicts inducibility of ventricular tachycardia in patients with syncope of unknown origin: a prospective study. *J. Am. Coll. Cardiol*. 10:775–781, 1987.

A.60 STEINBERG JS, PRYSTOWSKY E, FREEDMAN RA, ET AL. Use of the signal-averaged electrocardiogram for predicting inducible ventricular tachycardia in patients with unexplained syncope; relation to clinical variables in a multivariate analysis. *J. Am. Coll. Cardiol*. 23:99–106, 1994.

A.61 BUXTON AE, SIMSON MB, FALCONE RA, ET AL. Results of signal-averaged electrocardiography and electrophysiologic study in patients with nonsustained ventricular tachycardia after healing of acute myocardial infarction. *Am. J. Cardiol*. 60:80–85, 1987.

A.62 WINTERS SL, IP J, DESHMUKH P, ET AL. Determinants of induction of ventricular tachycardia in nonsustained ventricular tachycardia after myocardial infarction and the usefulness of signal-averaged electrocardiogram. *Am. J. Cardiol*. 72:1281–1285, 1993.

A.63 TURITTO G, FONTAINE JM, URSELL SN, ET AL. Value of the signal-averaged electrocardiogram as a predictor of the results of programmed stimulation in nonsustained ventricular tachycardia. *Am. J. Cardiol*. 61:1272–1278, 1988.

A.64 CAIN M.E., ET AL. Fast-Fourier transform analysis of signal-averaged electrocardiograms for identification of patients prone to sustained ventricular tachycardia. *Circulation.*. 69:711–720, 1984.

A.65 LINDSAY B.D., ET AL. Improved differentiation of patients with and without ventricular tachycardia by frequency analysis of multiple electrocardiographic leads. *Am. J. Cardiol*. 62:556–561, 1988.

A.66 LINDSAY B.D., ET AL. Identification of patients with sustained ventricular tachycardia by frequency analysis of signal-averaged electrocardiograms despite the presence ofbundle branch block. *Circulation* 77:122–130, 1988.

A.67 MACHAC J., ET AL. A comparative study of frequency domainand time domain analysis of saecgs in patients with ventricular tachycardia. *J. Am. Coll. Cardiol*.11:284–296, 1988.

A.68 LANDER P, BERBARI EJ, ET AL. Time-frequency analysis of ventricular late potentials. *J. of Electrocardiology*. (Suppl.) 1988, S80.

A.69 LANDER P, ALBERT DE, and BERBARI EJ. Spectrotemporal analysis of ventricular late potentials. *J. of Electrocardiology*. 23:95–108, 1990.

A.70 PIERCE DL, EASLEY AR, WINDLE JR and ENGEL TR. Fast Fourier transformation of entire low amplitude late QRS potential to predict ventricular tachycardia. *J. Amer. Coll. Cardiol*. 14:1731–1740, 1989.

A.71 CAIN M.E., ET AL. Spectral and temporal interrogation of SAECG : The best is yet to come. (Editorial) *J. Am. Coll. Cardiol*.14:1741–1743, 1989.

A.72 BUCKINGHAM TA., ET AL. SAECG in time and frequency domains. *Am. J. Cardiol*. 63:820–825, 1989.

A.73 WORLEY SJ., ET AL. Comparison of time domain and frequency domain variables from the signal-averaged ECG: A multivariable analysis. *JACC*. 11:1041–1051, 1988.

A.74 HABERL R., ET AL. Comparison of frequency and time domain analysis of the saecg in patients with ventricular tachycardia and coronary artery disease: methodologic validation and clinical relevance. *JACC*. 12:150–158, 1988.

A.75 HABERL R., ET AL. Spectral mapping of ECG with Fourier transform for identification of payients with sustained ventricular tachycardia and coronary artery disease. *Eur. Heart J*. 10:316–322, 1989.

A.76 HABERL R., ET AL. Top-resolution frequency analysis of ECG with adaptive frequency determination: Identification of late potentials in patients with coronary artery disease. *Circulation* 82: 1183–1192, 1990.

A.77 CAIN ME., ET AL. Diagnostic implications of spectral and temporal analysis of the entire cardiac cycle in patients with ventricular tachycardia. *Circulation* 83:1637–1648, 1991.

A.78 KELEN GJ., ET AL. Spectral turbulence analysis of SAECG and its predictive accuracy for inducible sustained monomorphic ventricular tachycardia. *Amer. J. Cardiol*. 67:965–975, 1991.

A.79 MALIK M, KULAKOWSKI P, POLONIECKI J, STAUNTON A, ODEMUYIWA O, FARRELL T, and CAMM J. Frequency versus time domain analysis of signal-averaged ECGs. I. Reproducibility of results. *J. Amer. Coll. Cardiol*. 20:127–134, 1992.

A.80 KULAKOWSKI P, MALIK M, POLONIECKI J, BASHIR Y, ODEMUYIWA O, FARRELL T, STAUNTON A, and CAMM J. Frequency versus time domain analysis of signal-averaged ECGs. II. Identification of patients with ventricular tachycardia after myocardial infarction. *J. Amer. Coll. Cardiol*. 20:135–143, 1992.

A.81 ODEMUYIWA O, MALIK M, POLONIECKI J, FARRELL T, KULAKOWSKI P, STAUNTON A, and CAMM J. Frequency versus time domain analysis of signal-averaged ECGs. III. Stratification of postinfarction for arrhythmic events. *J. Amer. Coll. Cardiol*. 20:144–150, 1992.

A.82 MORLET D., ET AL. Wavelet analysis of high-resolution ECGs in postinfarction patients: role of the basic wavelet and of the analyzed lead. *Int. L. Biomed. Comput*. 39:311–316, 1995.

A.83 COUDERC JP., ET AL. Stratification of time-frequency abnormalities in the signal-averaged high resolution ECG in postinfarction patients with and without ventricular tachycardia and congenital long QT syndrome. *J. Electrocardiol*. 29 (suppl.):180–188, 1996.

A.84 ROSENHECK S. Signal-averaged P wave in patients with paroxysmal atrial fibrillation. *Pacing Clin. Electrophysiol*. 20(10 Pt 2):2577–2586, Oct. 1997.

A.85 ABE Y, FUKUNAMI M, YAMADA T, OHMORI M, SHIMONAGATA T, KUMAGAI K, KIM J, SANADA S, HORI M, and HOKI N. Prediction of transition to chronic atrial fibrillation in patients with paroxysmal atrial fibrillation by signal-averaged electrocardiography: a prospective study. *Circulation* 96(8):2612–2616, Oct. 21 1997.

A.86 OPOLSKI G, SCISLO P, STANISLAWSKA J, GORECKI A, STECKIEWICZ R, and TORBICKI A. Detection of patients at risk for recurrence of atrial fibrillation after successful electrical cardioversion by signal-averaged P-wave ECG. *Int. J. Cardiol*. 60(2):181–185, July 25 1997.

A.87 CECCHI F, MONTEREGGI A, OLIVOTTO I, MARCONI P, DOLARA A, and MARON BJ. Risk for atrial fibrillation in patients with hypertrophic cardiomyopathy assessed by signal averaged P wave duration. *Heart* 78(1):44–49, July 1997.

A.88 ZAMAN AG, ALAMGIR F, RICHENS T, WILLIAMS R, ROTHMAN MT, and MILLS PG. The role of signal averaged P wave duration and serum magnesium as a combined predictor of atrial fibrillation after elective coronary artery bypass surgery. *Heart* 77(6):527–531, June 1997.

A.89 STAFFORD PJ, and VINCENT R. Spectrotemporal and spectral turbulence analysis of the signal-averaged P wave in paroxysmal atrial fibrillation. *J. Electrocardiol*. 30(2):79–86, April 1997.

A.90 STAFFORD PJ, KOLVEKAR S, COOPER J, FOTHERGILL J, SCHLINDWEIN F, DEBONO DP, SPYT TJ, and GARRATT CJ. Signal averaged P wave compared with standard electrocardiography or echocardiography for prediction of atrial fibrillation after coronary bypass grafting. *Heart* 77(5):417–422, May 1997.

A.91 GUIDERA SA, and STEINBERG JS. The signal-averaged P wave duration: A rapid and noninvasive marker of risk atrial fibrillation. *J. Am. Coll. Cardiol*. 21:1645–1651, 1993.

A.92 FUKUNAMI M, YAMADA T, OHMORI, ET AL. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave-triggered signal-averaged electrocardiogram. *Circulation* 83:162–169, 1991.

A.93 STAFFORD PJ, TURNER I, VINCENT R. Quantitative analysis of signal-averaged P waves in idiopathic paroxysmal atrial fibrillation. *Am. J. Cardiol*. 68:751–755, 1991.

A.94 STEINBERG JS, ZELENKOFSKE S, WONG S, ET AL. Value of the P-wave signal-averaged ECG for predicting atrial fibrillation after cardiac surgery. *Circulation* 88:2618–2622, 1993.

Annex B
(informative)

Additional reading

BREITHARDT G, CAIN ME, EL-SHERIF N, FLOWERS NC, HOMBACH V, JANSE M, SIMSON MB, and STEINBECK G. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography: a statement by a task force committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. *J. Am. Coll. Cardiol.* 17(5): 999–1006. April 1991.

DECHILLOU C, RODRIGUEZ LM, DOERENDANS P, ET AL. Effects on the signal-averaged electrocardiogram of opening the coronary artery by thrombolytic therapy or percutaneous transluminal coronary angioplasty during acute myocardial infarction. *Am. J. Cardiol*. 71:805–809, 1993.

DHALA A, UNDERWOOD D, MADU E, and ANGEL J. Sex-specific differences in the P wave signal-averaged ECG. *J. Electrocardiol*. 30 Suppl:34–35, 1998.

EHLERT FA, KORENSTEIN D, and STEINBERG JS. Evaluation of P wave signal-averaged electrocardiographic filtering and analysis methods. *Am. Heart J*. 134(6):985–993, Dec. 1997.

EL-SHERIF N, and TURITTO G. *High Resolution Electrocardiography.* Futura: New York, 1992.

FAGGIANO P, D'ALOIA A, ZANELLI E, GUALENI A, MUSATTI P, and GIORDANO A. Contribution of left atrial pressure and dimension to signal-averaged P-wave duration in patients with chronic congestive heart failure. *Am. J. Cardiol*. 79(2):219–22, Jan. 15 1997.

GOMES A. *Signal Averaged Electrocardiography - Concepts, Methods and Applications*. Kluwer Academic Publishers: London, 1993.

MALIK M, KULAKOWSKI P, ODEMUYIWA O, ET AL. Effect of thrombolytic therapy on the predictive value of signal-averaged electrocardiography after acute myocardial infarction. *Am. J. Cardiol*. 70:21–25, 1992.

MORENO FL, KARAGONIS LA, VILLANUEVA T, HORN SD, and ANDERSON JA. Comparison of signal-averaging Electrocardiographic systems using device-specific criteria on 104 normal subjects. *Pacing and Clinical Electrophysiol (PACE)* 17 (Pt. 111): 2178-2182, 1994.

Signal-averaged electrocardiography. (ACC Expert Consensus Document). *J Am Coll Cardiol.* 27:238-49. 1996.

STAFFORD PJ, COOPER J, BAKER S, DEBONO DP, VINCENT R, and GARRATT CJ. The signal averaged P wave in atrioventricular block–evidence for abnormal atrial conduction. *Int. J. Cardiol*. 63(2):155–159, Jan. 31 1998.

STAFFORD PJ, COOPER J, FOTHERGILL J, SCHLINDWEIN F, DEBONO DP, and GARRATT CJ. Reproducibility of the signal averaged P wave: time and frequency domain analysis. *Heart* 77(5):412–6., May 1997.

TAMIS JE, and STEINBERG JS. Value of the signal-averaged P wave analysis in predicting atrial fibrillation after cardiac surgery. *J. Electrocardiol*. 30 Suppl:36–43, 1998.

UNDERWOOD D, YAKUBO S, and OZAWA Y. Comparison of signal averaged ECG systems using device specific criteria (abstract). *IL COURE.* 10(suppl): 373, 1993.

VALVERDE ER, QUINTEIRO RA, BERTRAN GC, ARINI PD, GLENNY P, and BIAGETTI MO. Influence of filtering techniques on the time-domain analysis of signal-averaged P wave electrocardiogram. *J.* Cardiovasc. Electrophysiol. (3):253–60, Mar. 9 1998.

