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ACC EXPERT CONSENSUS DOCUMENT

Signal-Averaged Electrocardiography

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Preamble

The present document is an expert consensus. This type of document is intended to inform practitioners, payers and other interested parties of the opinion of the American College of Cardiology (ACC) concerning evolving areas of clinical practice and/or technologies that are widely available or are new to the practice community. Topics chosen for coverage by Expert Consensus Documents are so designated because some or all of the evidence base and experience with the technology or clinical practice are not sufficiently well developed to be evaluated by the formal ACC/AHA Practice Guidelines process. Thus, the reader should view the Expert Consensus Documents as the best attempt of the ACC to inform and guide clinical practice in areas in which rigorous evidence is not yet available. Where feasible, Expert Consensus Documents will include indications and contraindications. Some topics covered by Expert Consensus Documents will be addressed subsequently by the ACC/AHA Practice Guidelines process.

Topics for clinical practice guidelines and technology assessments are chosen by the ACC Technology and Practice Executive Committee (TPEC) on the basis of input solicited from ACC membership and leadership, other medical specialty societies, government and the health care industry. This committee, in its biannually updated Master Plan, selects and prioritizes appropriate topics, determines the optimal document type (i.e., Practice Guidelines, Expert Consensus Document or Policy Statement) and identifies the specific ACC committee that will take principal responsibility for forming the writing group. On approval of the Master Plan by the ACC Board of Trustees, the TPEC assigns each Expert Consensus Topic to an ACC committee chair, who submits a proposed writing group that includes content experts, clinician generalists and clinicians with health service research expertise. The draft of each Expert Consensus Document is evaluated by at least three external anonymous reviewers and revised as necessary before submission for TPEC approval. Of these documents, only those that pass the biannual TPEC review process are submitted to the ACC Board of Trustees for final review and approval.

The writing group for this Expert Consensus Document on signal-averaged electrocardiography was Michael E. Cain, MD, Chair, Jeffrey L. Anderson, MD, Morton F. Arnsdorf, MD, Jay W. Mason, MD, Melvin M. Scheinman, MD and Albert L. Waldo, MD.

Introduction

More than 400,000 Americans die suddenly each year from sustained ventricular tachycardia or ventricular fibrillation. Most have coronary artery disease and left ventricular dysfunction. Essential to reducing the incidence of sudden cardiac death is the accurate identification of patients at high risk.

Results of laboratory (1–3) and clinical (4,5) studies implicate reentrant mechanisms, at least in part, in the genesis of sustained ventricular tachycardia complicating ischemic heart disease. Clinically, most myocardial infarctions do not result in complete transmural necrosis. The amount of surviving myocardium varies and may be located in subepicardial, subendocardial or intramural regions. The increased separation of myocardial bundles and the disruption of their parallel orientation by fibrosis distort ventricular activation (6). When individual bundles are separated by connective tissue septa, heterogeneous patterns of activation occur and result in fragmentation of local extracellular electrograms. During sinus rhythm, delayed ventricular activation, often extending beyond the end of the QRS complex, is more profound and detectable at more cardiac sites in patients with than without sustained ventricular tachycardia (7,8).

Driven by the need to improve the noninvasive identification of patients susceptible to reentrant ventricular tachycardia, several signal-processing techniques for interrogating the terminal QRS complex and ST segment of the electrocardiogram (ECG) have been developed over the past 15 years. The goal of these signal-averaged ECG techniques is to detect

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occult derangements of ventricular activation, or late potentials, present during sinus rhythm that appear to be a hallmark for sustained ventricular arrhythmias (9–14). In 1990, the European Society of Cardiology, the American Heart Association and the ACC convened a joint Task Force to establish standards for acquisition and analysis of signal-averaged ECG data and to begin to define the role of this diagnostic method in clinical decision making.

Since publication of the task force committee's statement in 1991 (15), several signal-averaged ECG systems have been marketed, and a Current Procedural Terminology (CPT) code has been established for billing both technical and professional components. The present Expert Consensus Document focuses on updating the methods of signal processing that have been used to extract distinguishing ECG features, the indications for signal-averaged ECG analysis on patient care and the possibilities for continued refinement of techniques based on an increased understanding of the pathophysiologic basis of sustained ventricular tachycardia in humans.

Description and Analysis of Technology

Signal Averaging

The "noise" in orthogonal ECGs ranges from 8 to 10 μV and is generated primarily by skeletal muscle activity. The temporal and spectral features of ECGs that identify patients with ventricular tachycardia are masked by this level of noise. The purpose of signal averaging is to improve the signal-to-noise ratio to facilitate the detection of low-amplitude bioelectric potentials. Signals may be averaged by temporal or spatial techniques. Available commercial systems use temporal averaging, which reduces random or uncorrelated noise by the square root of the number of waveforms averaged (16). The following requirements must be met for temporal averaging to work effectively. First, the signal of interest must be repetitive and invariable. Time varying signals, such as ectopic or premature complexes, are eliminated before averaging by comparing incoming signals against a previously established template with the use of a cross-correlating technique. Second, the signal of interest must be time-locked to a fiducial point, such as the peak of the QRS complex, that is easily detectable and serves as a timing reference for the averaging algorithm. If the signal of interest does not have a fixed, temporal relationship with the timing reference point, the resultant averaged signal will be filtered and distorted due to reference jitter, with subsequent loss of the high-frequency components. Third, the signal of interest and the noise must be independent and remain independent during averaging. Current systems reduce noise to <1.0 μV.

Time-Domain Analysis

Most signal processing systems use time-domain analysis to detect late potentials in the terminal QRS complex. Detection of these microvolt waveforms, which are continuous with the QRS complex, requires high-gain amplification and appropriate digital filtering to reject low frequencies associated with the plateau and repolarization phases of the action potential, ST segment and T wave. This enhances detection of the high frequency signals that correspond to ventricular activation.

The passband and characteristics of the filter are crucial to time-domain results. A linear, shift-invariant (time-invariant) digital filter may be implemented in the time domain as a difference equation or as a convolution sum. If the filter is described by a rational polynomial, such as a Butterworth, Chebyshev or Bessel polynomial, then a difference equation provides a very efficient implementation. Unfortunately these filters have nonlinear phase characteristics. They not only change the amplitude of the ECG frequencies, but also shift frequency components relative to one another. To avoid phase distortion with these filters, bidirectional processing must be used. One half of the signal is passed through a Butterworth or similar polynomial filter. The second half of the signal is then reversed along the time axis and passed through the filter again. Filtering without phase distortion can be done in a single processing step with a linear phase filter that is implemented as a convolution sum. These filters are optimal because they minimize the maximal error between the actual and desired filter characteristics for a given number of samples in the impulse response of the filter.

Most systems use a bidirectional filter derived from a four-pole Butterworth. Orthogonal, bipolar XYZ ECG leads are recorded, averaged, filtered and combined into a vector magnitude called the *filtered QRS complex*. Analysis of the filtered QRS complex typically includes 1) the filtered QRS duration; 2) the root-mean-square voltage of the terminal 40 ms of the filtered QRS; and 3) the duration that the filtered QRS complex remains <40 μV. Values of these measurements are dependent on the high pass corner frequency. Filter frequencies of 25 to 100 Hz have been investigated; most recent systems use a 40-Hz high-pass filter.

Characteristics of a late potential (assuming use of a 40-Hz high-pass bidirectional filter) include 1) a filtered QRS complex >114 ms; 2) a signal <20 μV in the last 40 ms of the filtered QRS complex; and 3) voltage <40 μV in the terminal QRS complex for >38 ms (17).

Frequency-Domain Analysis

A sequence generated by sampling a time-domain signal like the ECG can be represented in the frequency domain by use of its Fourier transform. There are three Fourier transforms that are used to represent a signal: 1) the continuous transform of a continuous signal, 2) the continuous transform of the samples of that signal and 3) the discrete transform of the samples. The Fourier transform of a continuous signal is defined by an integral involving that signal over time. The Fourier transform of the samples of a continuous signal is a scaled version of the continuous signal transform, as long as the samples are taken at a rate at least twice the highest frequency present in the signal. The discrete Fourier transform samples the scaled, continuous Fourier transform. The fast

Fourier transform is an algorithm for calculating the discrete Fourier transform that decomposes a complex periodic waveform such as the ECG into a sum of harmonically related sinusoids. Each harmonic is characterized by its frequency, magnitude and phase.

Key features in the spectra of signal-averaged ECGs elicited by derangements of ventricular activation, including late potentials, have been identified that distinguish patients prone to sustained ventricular arrhythmias (18,19). Most studies have calculated scalar-lead spectra of portions of the terminal QRS complex and ST segment of individual Frank X, Y and Z leads. Results have often been expressed as indexes of the relative contributions of 20- to 50-Hz frequencies that comprise these ECG segments (18,19).

To analyze a portion of the ECG, such as the terminal QRS complex or ST segment, data intervals must first be multiplied by a window function to reduce spectral leakage because the initial and final data points are not isopotential (20). Multiplication of a signal by a window function in the time domain is equivalent to convoluting the Fourier transform of the signal with the transform of the window function. Because convolution is a linear operation, the ECG frequency components may be convoluted with the window transform individually and the results summed. Convolution with a given frequency component produces a replica of the window transform. Thus, to separate or resolve two equal-strength frequency components or lines in a windowed spectrum, the lines must be far enough apart to separate two versions of the window spectrum. The same effect is seen with the direct-current component in the segment before windowing. It also produces a replica of the window spectrum around the zero-frequency (direct current) line in the transform of the windowed segment. The spectrum of a window function consists of a main band and side lobes. The resolution, or ability to separate spectral features at adjacent frequency lines, of a window function is related to the narrowness of its main band. Smearing, or spectral leakage, of the spectral estimate is related to the width of the main band of the window as well as the magnitude of its side lobes. This relation between the main band and the side lobes represents a signal-processing trade-off because even windows with the most narrow main bands have side lobes of considerable magnitude. Accordingly, care must be taken to select a window function that allows detection of nearby components of significantly different amplitudes without compromising resolution, dynamic range or ease of implementation. Most studies have used a four-term Blackman-Harris window to compute the spectrum of the terminal 40 ms of the QRS complex and ST segment (data interval of approximately 150 ms). The main lobe of the spectrum of a 150-ms, four-term Blackman-Harris window is down 7 dB at 10 Hz, down 33 dB at 20 Hz, and by 27 Hz has reached its 94-dB floor. Its 3-dB resolution is 13 Hz.

In addition to the fast Fourier transform, other methods of estimating the spectra of short ECG segments have been used, including moving time window techniques, such as spectrotemporal mapping (21,22) and spectral turbulence analysis (23), and autoregressive methods, including maximal entropy (24) and adaptive frequency determination (25). Technique selection is based on information sought. The fast Fourier transform with a window function is suitable if identification of frequency bands, but not of specific frequency peaks, is required. However, if spectral peaks and timing information are required, moving time window and autoregressive methods must be used. End points of spectral analysis have not yet been standardized.

Clinical Outcomes and Recommendations for Use of Signal-Averaged ECG

The sections that follow summarize the data acquired from key clinical studies and serve as the basis for current recommendations for the use of the signal-averaged ECG in patients. Although many published reports describe the performance of evolving time- and frequency-domain methods of analyzing the signal-averaged ECG recorded from patients with ventricular arrhythmias and a variety of heart diseases, there is a paucity in some clinical areas of prospective studies that examine clinical outcomes. Accordingly, the committee considered that publishing recommendations for the use of the signal-averaged ECG in some clinical areas is premature and that additional information as well as refinements in methods of data analysis are desirable before firm indications can be established. Recommendations for the use of the signal-averaged ECG are discussed in the sections that follow and are highlighted in Table 1.

Patients With Ischemic Heart Disease and Sustained Ventricular Arrhythmias

The incidence of abnormalities detected in signal-averaged ECGs recorded from normal subjects, patients with healed myocardial infarction and sustained ventricular arrhythmias and patients with healed infarction without sustained ventricular arrhythmias are summarized in Table 2 (11–14,21–30). Most studies have focused on patients with sustained monomorphic ventricular tachycardia. Despite differences in methods of data acquisition and analysis, the results obtained have been concordant. Temporal and spectral abnormalities in the signal-averaged ECG are detected rarely in normal subjects, in only a small percentage of patients who have had myocardial infarction but not ventricular tachycardia and in up to 93% of patients with a history of sustained monomorphic ventricular tachycardia.

Most reports to date have evaluated signal-averaged ECGs obtained from patients during sinus rhythm in the absence of bundle branch block or marked intraventricular conduction abnormalities. Sufficient data are not yet available using end points of time-domain analysis to establish criteria in patients manifesting right or left bundle branch block during sinus rhythm (31). The differentiation of patients with from those without ventricular tachycardia by spectral analysis of signal-averaged ECGs is not affected by the presence of bundle branch block during sinus rhythm, suggesting that occult

Table 1. Recommendations for Use of Signal-Averaged Electrocardiogram

Established value
- Stratification of risk of development of sustained ventricular arrhythmias in patients recovering from myocardial infarction who are in sinus rhythm without electrocardiographic evidence of bundle branch block or intraventricular conduction delay (QRS complex >120 ms)
- Identification of patients with ischemic heart disease and unexplained syncope who are likely to have inducible sustained ventricular tachycardia

Valuable in clinical care, further supportive evidence desirable
- Stratification of risk of development of sustained ventricular arrhythmias in patients with nonischemic cardiomyopathy
- Assessment of success of operation for sustained ventricular tachycardia

Promising but currently unproved
- Detection of acute rejection of heart transplants
- Assessment of efficacy or proarrhythmic effects of antiarrhythmic drug therapy in patients with ventricular arrhythmias
- Assessment of success of pharmacologic, mechanical or surgical interventions to restore coronary artery blood flow

Not indicated
- Patients with ischemic heart disease and documented sustained ventricular arrhythmias
- Stratification of risk of development of sustained ventricular arrhythmias in asymptomatic patients without detectable heart disease

Table 2. Incidence of Abnormalities on Signal-Averaged Electrocardiogram*

Study Groups	Incidence (%)	
	TD	FD
Normal subjects	0–10	4
Recent MI (<2 wk), no VT	14–29	26
Remote MI (≥1 mo), no VT	18–33	23
Remote MI (≥1 mo), VT	52–90	73–92

*Based on data from references 11 to 14 and 21 to 30. FD = frequency domain; MI = myocardial infarction; TD = time domain; VT = ventricular tachycardia.

derangements in ventricular conduction and total duration of ventricular activation are not the only important determinants of risk for developing life-threatening ventricular arrhythmias (18).

In contrast to patients with sustained monomorphic ventricular tachycardia, late potentials are detectable in signal-averaged ECGs from only 21% to 65% of patients with ischemic heart disease and ventricular fibrillation (32–34). However, alterations in the magnitude spectra of signal-averaged ECGs from patients with ventricular fibrillation and those with ventricular tachycardia are detectable to a similar extent (19).

Recommendations for use of signal-averaged ECG. Results of analysis of the signal-averaged ECG recorded during sinus rhythm using currently available time- and frequency-domain methods have not yet been shown to have an impact on the prognosis or the selection of antiarrhythmic interventions for individual patients with healed myocardial infarction and documented sustained ventricular tachycardia or fibrillation. On the basis of available data, the consensus of the committee is that the recording of a signal-averaged ECG in these patients is, at present, of no clinical value. Further investigation is required in patients with coronary artery disease but without myocardial infarction who survive ventricular tachycardia or ventricular fibrillation to determine whether the finding of a normal signal-averaged ECG accurately identifies those likely to benefit from interventions that improve coronary blood flow but do not require pharmacologic or nonpharmacologic antiarrhythmic therapy.

Patients Recovering From Myocardial Infarction

Abnormalities in the signal-averaged ECG have been determined to be independent predictors of risk of developing ventricular arrhythmias in patients convalescing from myocardial infarction (Table 3) (35–51). Late potentials have been detected in signal-averaged ECGs from 39% to 93% of patients recovering from acute myocardial infarction who ultimately suffer sustained ventricular arrhythmias or sudden cardiac death. Among these patients with late potentials, 8% to 48% will develop sustained ventricular tachycardia or sudden death. In most studies, less than 5% of patients with normal signal-averaged ECGs have these complications. Thus, the signal-averaged ECG has excellent negative predictive accuracy when used to assess risk for development of life-threatening ventricular arrhythmias. *However, the positive predictive accuracy of the signal-averaged ECG alone is not yet sufficiently powerful to justify interventions in individual patients in whom results of analysis are abnormal.*

In Table 4, the performance of the signal-averaged ECG is compared with that reported for other diagnostic tests used clinically to stratify risk for development of sustained ventricular arrhythmias or sudden cardiac death in patients recovering from myocardial infarction. Importantly, the accuracy of risk stratification is improved (Table 5) when the signal-averaged ECG is combined with left ventricular ejection fraction, degree of ventricular ectopic activity, heart rate variability or response to programmed ventricular stimulation (36–42,47,48,52).

Recommendations for use of signal-averaged ECG. On the basis of available data, the consensus of the Committee is that the signal-averaged ECG is of established value in stratifying risk of developing a sustained ventricular arrhythmia in patients without bundle branch block or marked (≥120 ms) intraventricular conduction delays who are recovering from myocardial infarction. A normal signal-averaged ECG indicates a low risk for developing life-threatening ventricular arrhythmias. The probability of sustained ventricular tachycardia or sudden death in an individual patient will be influenced by the number of risk factors. The established negative predictive accuracy of 95% to 99% has substantial clinical value in

Table 3. Prognostic Value of Signal-Averaged Electrocardiograms for Defining Risk for Development of Ventricular Tachycardia or Sudden Death After Myocardial Infarction

Study (ref no.)	No. of Pts	Pts Treated With Thrombolytic Agents (%)	Sensitivity (%)	Specificity (%)	Predictive Value (%)	
					Positive	Negative
Breithardt et al. (43)	160	NA	63	72	17	96
Cripps et al. (41)	176	NA	82	81	22	99
Denniss et al. (37)	403	NA	65	77	19	96
El-Sherif et al. (42)	156	NA	75	79	23	97
Gomes et al. (38)	102	NA	87	63	29	96
Kuchar et al. (40)	200	NA	93	65	17	99
Kuchar et al. (36)	157	NA	92	62	17	99
Rodriguez et al. (44)	190	NA	39	91	48	88
Steinberg et al. (45)	182	NA	69	64	15	95
Verzoni et al. (46)	220	NA	83	73	8	99
Farrell et al. (47)	416	48	63	81	17	81
Pedretti et al. (48)	303	54	63	77	16	97
McClements et al. (49)	301	68	64	81	11	98
Zimmermann et al. (50)	223	26	67	80	16	98
Pedretti et al. (51)	174	39	75	82	18	98

NA = not available; Pts = patients; ref = reference.

these patients because it obviates the need for additional diagnostic tests in those with other single risk factors, such as ventricular ectopic beats or moderate to severe left ventricular dysfunction, making the signal-averaged ECG cost-effective in this setting (Tables 4 and 5). The negative predictive accuracy of a normal signal-averaged ECG in a patient with two or more risk factors has not yet been established definitively. Its present positive predictive accuracy of only 14% to 29%, however, militates against its use alone to determine whether medical intervention is necessary in a given patient with ischemic heart disease. Management strategies for patients recovering from myocardial infarction with abnormal responses on the signal-averaged ECG and/or other tests (Table 5) are not yet established. Controlled studies are in progress to determine whether a combination of the signal-averaged ECG and programmed ventricular stimulation can identify high-risk patients whose risk of sudden death can be reduced by treatment with antiarrhythmic drugs or implantation of a cardioverter-defibrillator (53).

Patients With Nonischemic Heart Disease

Findings from some (54–56) but not all (57–63) studies of patients with dilated nonischemic cardiomyopathy have indicated that results of time-domain analysis of the signal-averaged ECG correlate with the occurrence of ventricular arrhythmias and clinical outcome. On the basis of results of prospective studies, time-domain analysis of the signal-averaged ECG has a sensitivity of 71% to 100%, a specificity of 66% to 86%, a negative predictive accuracy of 94% to 100% and a positive predictive accuracy of 25% to 45% (55,56).

Table 4. Incidence of Sustained Ventricular Arrhythmias or Sudden Cardiac Death in Patients After Myocardial Infarction*

Test and CPT Code	Percent Adverse Outcome		Global Payment Allowed, 1995 Medicare Fee Schedule (dollars)
	For Normal Test Results	For Abnormal Test Results	
SAECG			
93728	1–3	17–29	75.47
Ejection fraction			
93307 (echo)	5–6	16–24	201.50
78472 (MUGA)			245.11
Holter Monitor			
93224	7–9	14–23	165.48
HRV			
N/A	1–23	16–17	N/A
Programmed stimulation			
93620	0–4	12–32	1,218.97

*Based on data from references 36, 42 , 47, 48, 52. Echo = echocardiography; HRV = heart rate variability; MUGA = multiple gated acquisition ventriculogram; NA = not available; SAECG = signal-averaged electrocardiogram.

Table 5. Incidence of Documented Sustained Ventricular Arrhythmias or Sudden Cardiac Death in Patients After Myocardial Infarction*

Test†	Percent Adverse Outcomes		Total Costs (dollars)	
	For Normal Test Results	For Abnormal Test Results	LVEF by Echo	LVEF by MUGA
SAECG and ejection fraction	0–1	31–38	276.97	320.58
SAECG and Holter monitor	0–1	27–35	240.95	
Ejection fraction and Holter monitor	7	29	366.98	410.59
SAECG, ejection fraction and Holter monitor	0	50	442.45	486.06
SAECG and programmed stimulation	2	27	1,294.44	
SAECG and HRV	7	33	75.47‡	
SAECG, HRV and Holter monitor	4	43	240.95‡	

*Based on data from references 36, 42, 47, 48, 52. †CPT codes as in Table 4. ‡Currently, there is no CPT code to bill for this service; therefore, no additional charges are built into the total costs. Ejection fraction = <40% (see Table 4 for measuring ejection fraction included in cost analysis); Total Costs = global payments allowed for these combinations of services in the 1995 Medicare fee schedule (national average, full fee schedule payment) utilizing total relative values and the 1995 conversion factor for nonsurgical services. Abbreviations as in Table 4.

The incidence of altered frequency components in signal-averaged ECGs from patients with nonischemic or ischemic heart disease is similar, even when patients with ventricular tachycardia or ventricular fibrillation are considered separately (19). The predictive value of spectral analysis of the signal-averaged ECG is superior to that of programmed stimulation in patients with dilated nonischemic cardiomyopathy.

Recommendations for use of signal-averaged ECG. On the basis of the available data, the consensus of the committee is that the signal-averaged ECG is valuable in clinical care of patients with dilated cardiomyopathies, but further supportive evidence is desirable before the use of the signal-averaged ECG in these patients can be definitely recommended.

Abnormalities have also been detected in signal-averaged ECGs from patients with left ventricular hypertrophy (61–64), arrhythmogenic right ventricular dysplasia (65,66), idiopathic ventricular tachycardia (67,68), Duchenne-type muscular dystrophy (69), myotonic muscular dystrophy (70), systemic sclerosis (71), mitral valve prolapse (72), diabetes (73), mitoxantane cardiotoxicity (74) and human immunodeficiency virus infection (75), as well as after surgical repair of congenital heart disease, especially tetralogy of Fallot (76,77). Prospective studies to determine the clinical impact of these observations have not yet been performed.

Patients With Syncope

Patients with unexplained syncope are often referred for electrophysiologic studies to determine whether sustained ventricular tachycardia can be induced. A noninvasive screening test that accurately identified those patients in whom sustained ventricular tachycardia was induced would be desirable. Table 6 summarizes the concordance between the results of signal-averaged ECG analysis and the induction of sustained monomorphic ventricular tachycardia by programmed stimulation in patients undergoing electrophysiologic studies for documented or suspected sustained ventricular tachycardia (78–83). Several clinical factors, including left ventricular ejection fraction, history of myocardial infarction and complexity of ventricular ectopic activity, when used along with results of signal-averaged ECG analysis, improve the prospective identification of patients with inducible sustained ventricular tachycardia.

The results summarized in Table 6 are from patients who were specifically selected for electrophysiologic testing. In comparison, Kuchar et al. (84) evaluated 150 consecutive patients with syncope. Late potentials were detectable in the signal-averaged ECGs from 29 patients (21%), 16 of whom were found to have ventricular tachycardia. The signal-

Table 6. Value of Signal-Averaged Electrocardiograms for Predicting Inducibility of Sustained Ventricular Tachycardia in Patients Without Spontaneous Sustained Ventricular Arrhythmias

Study (ref no.)	Analysis	No. of Pts	Sensitivity (%)	Specificity (%)	Predictive Value (%)	
					Positive	Negative
Nalos et al. (79)	TD	62	100	96	83	100
Turitto et al. (82)	TD	105	66	89	66	89
Vatterott et al. (80)	TD	214	84	54	47	88
Winters et al. (81)	TD	34	92	68	61	93
Gang et al. (83)	TD	24	89	100	100	94
Lindsay et al. (78)	FD	62	78	56	52	90

Abbreviations as in Tables 2 and 3.

averaged ECG response was normal in each of 101 patients with syncope that was attributed to causes other than ventricular tachycardia. In that study, the signal-averaged ECG had a sensitivity of 73%, specificity of 55%, positive predictive value of 55% and negative predictive value of 94%. Lacroix et al. (85) studied 100 patients who presented with syncope and underwent electrophysiologic testing. They determined that the positive predictive value of late potentials for predicting the inducibility of sustained monomorphic ventricular tachycardia was 39% (85). Overall, results of studies in patients with syncope demonstrate that the signal-averaged ECG is a sensitive diagnostic test with a positive predictive value of 40% to 83% and a negative predictive value of about 90%.

Recommendations for use of signal-averaged ECG. On the basis of the available data, the consensus of the committee is that the signal-averaged ECG is of established value in patients with ischemic heart disease and syncope. The clinical value of the signal-averaged ECG is in its negative predictive accuracy. A normal finding on the signal-averaged ECG in a patient with ischemic heart disease and syncope, in whom the suspicion for a ventricular arrhythmia is low, is supportive and may obviate the need for invasive electrophysiologic studies to determine whether sustained ventricular tachycardia is inducible. However, if the suspicion for a ventricular arrhythmia is high, a normal response on the signal-averaged ECG does not exclude ventricular tachycardia as a cause. At present, there are insufficient data to recommend that the signal-averaged ECG be used to direct the management of patients with nonischemic heart disease and syncope.

Determination of Success of Arrhythmia Surgery

Removal of part or all of the myocardium responsible for ventricular tachycardia is associated with a reduction in the incidence of late potentials detected in signal-averaged ECGs recorded after surgery (86–89). According to published studies, 85% to 100% of patients in whom sustained ventricular tachycardia remains inducible after surgery have late potentials detected in signal-averaged ECGs after surgery. Approximately 90% of the patients in whom results of signal-averaged ECG analysis are normal after surgery have no inducible ventricular tachycardia, but 56% of these patients continue to manifest abnormal signal-averaged ECG responses, presumably because areas of slow conduction remain despite resection of myocardial tissue critical to arrhythmogenesis.

Recommendations for use of signal-averaged ECG. On the basis of the available data, the consensus of the committee is that the signal-averaged ECG is considered to be valuable in assessing the success of operation for ventricular tachycardia, but further supportive evidence is desirable.

Prediction of Efficacy of Antiarrhythmic Drugs

Class IA, IC and III (90–103) but not IB (95–97) antiarrhythmic drugs elicit changes in the characteristics of ventricular late potentials. Not surprisingly, class IC drugs are associated with a more marked increase in the filtered QRS duration than are class IA agents (95).

In general, time-domain analysis of the signal-averaged ECG has not shown a correlation between the changes induced during drug therapy and antiarrhythmic drug efficacy (90,91,95,97,99,100). Some (92–94,98), but not all (95) studies have demonstrated a correlation between the prolongation of the total filtered QRS duration induced by class I antiarrhythmic drugs and prolongation of the cycle length of ventricular tachycardia.

A limitation of late potential analysis is the absence of information about ventricular repolarization or refractoriness. One study of patients with ischemic heart disease and ventricular tachycardia characterized the changes in the signal-averaged ECG, ventricular effective refractory period and corrected QT (QTc) interval elicited by procainamide (92). Prolongation in the ventricular effective refractory period and QTc correlated with drug efficacy (noninducibility), whereas an increase in the duration of the low-amplitude signal of the signal-averaged ECG correlated with a lengthening in the cycle length of the ventricular tachycardias that remained inducible. The ratio of drug-induced change in the QTc interval to the change in filtered QRS duration identified the patients with sustained ventricular tachycardia that remained inducible despite drug therapy.

Only a few studies have examined the effects of class III drugs. Amiodarone increased the filtered QRS duration, prolonged the late potential duration and decreased the root-mean-square voltage of the terminal QRS complex (102,103). In patients with ventricular ectopic beats, the changes in the signal-averaged ECG elicited by amiodarone did not correlate with drug efficacy (103). In contrast, prolongation of the filtered QRS duration in signal-averaged ECGs after treatment with sotalol in patients with sustained ventricular tachycardia was associated with a decreased likelihood of drug success, as assessed by programmed ventricular stimulation (100).

Frequency analysis of the signal-averaged ECG may enhance the detection of the drug-induced changes that are indicative of effective antiarrhythmic therapy. Interrogation of the terminal QRS/ST segment (104) or the entire cardiac cycle (105) has demonstrated changes in the magnitude spectra in successful drug trials. The sensitivity and specificity of spectral turbulence analysis in predicting efficacy of sotalol in patients with healed myocardial infarction and inducible monomorphic ventricular tachycardia were 86% and 70%, respectively (101). In contrast, a study of patients with inducible sustained ventricular tachycardia treated with procainamide found the results of spectral temporal mapping of the signal-averaged ECG to be similar before and after drug administration (93).

Recommendations for use of signal-averaged ECG. The potential of signal-averaged ECG analysis to define the efficacy of antiarrhythmic interventions is high. The observed effects of antiarrhythmic drugs on the signal-averaged ECG appear to be class specific and vary with the method of analysis. The development of indexes that provide an accurate noninvasive

assessment of antiarrhythmic drug efficacy remains an area of active investigation. On the basis of the available data, the consensus of the committee is that the signal-averaged ECG is considered a promising but currently an unproven method for assessing the efficacy or proarrhythmic effects of antiarrhythmic drug therapy in patients with ventricular arrhythmias.

Detection of Myocardial Ischemia or Myocardial Reperfusion

Analyses of signal-averaged ECGs obtained before, during and after myocardial ischemia induced by balloon angioplasty have demonstrated marked reduction of the root-mean-square voltage, changes in waveform configuration and increases in the duration of the low amplitude (<40 μV) signal comprising the terminal portion of the QRS complex but no significant changes in the duration of the filtered QRS complex (106,107). Late potentials were more likely to be detected in signal-averaged ECGs during balloon-induced ischemia in patients with a history of prior myocardial infarction (107). In contrast, changes in the signal-averaged ECG have not been consistently detected during clinical episodes of angina (108) or during ischemia induced by dipyridamole (109) or exercise (110–113). Thus, standard time-domain measures of the signal-averaged ECG are sensitive only to the electrophysiologic changes induced by profound ischemia.

Treatment of acute myocardial infarction with thrombolytic agents has been shown to decrease mortality. Most studies have reported a lower incidence of late potentials in signal-averaged ECGs (range 5% to 24%) from patients treated with thrombolytic agents than in in ECGs from patients not treated (range 18% to 43%) (114–124). In all these studies the diminished incidence of late potentials was attributable to the status of the infarct-related artery and not to left ventricular ejection fraction. The overall accuracy of time-domain analysis of the signal-averaged ECG for prediction of patency of the infarct-related artery has a sensitivity that ranges from 39% to 69% and a specificity that ranges from 47% to 91% (118,119).

Prompt reperfusion of the infarct-related artery by angioplasty has also been associated with a decrease in the incidence of late potentials. The incidence of late potentials in patients undergoing primary angioplasty for reperfusion at <4, 4 to 6, 6 to 8, 8 to 10 and >10 h after infarction was 8%, 12%, 14%, 33% and 43%, respectively (125). In contrast, late potentials were detected in the signal-averaged ECGs from 48% of the patients treated conventionally. However, the predictive value of late potentials for arrhythmic events after myocardial infarction in patients treated with primary angioplasty has not yet been established.

Restoration of myocardial perfusion by angioplasty in patients with chronic coronary artery disease has resulted in the resolution of abnormalities detected in the signal-averaged ECG in some (126) but not all (127), studies. The effect of coronary artery bypass grafting on the signal-averaged ECG has also been assessed in patients with chronic coronary artery disease (128). After surgery, detection of abnormalities in the signal-averaged ECG is rare in patients without a history of prior myocardial infarction; in patients with prior infarction, abnormalities may resolve or improve after surgery. The clinical impact of the changes detected in signal-averaged ECGs after myocardial reperfusion in patients with chronic coronary artery disease has not yet been defined.

Recommendations for use of signal-averaged ECG. On the basis of the available data, the consensus of the committee is that present methods of analyzing the signal-averaged ECG are promising but currently unproved for assessment of pharmacologic, mechanical or surgical interventions that restore coronary blood flow.

Detection of Cardiac Transplant Rejection

It is likely that the ECG footprint of an anatomic-electrophysiologic substrate for sustained ventricular tachycardia is different than the ECG abnormalities that accompany acute rejection of heart transplants. Accordingly, methods of analysis and indexes of abnormality have had to be defined de novo. Only a few studies have examined the extent to which changes detectable in signal-averaged ECGs are a measure of heart transplant rejection (129–132). An initial report of temporal analysis of the signal-averaged ECG showed a sensitivity of 65%, positive predictive accuracy of 92% and negative predictive accuracy of 68% for acute rejection (129). An 11% decrease in the root-mean-square voltage of the 70-Hz high-pass filtered QRS complex has been found to provide 88% sensitivity and 78% specificity for the presence of rejection (130).

An initial study of spectral analysis of the QRS complex demonstrated an increase in the magnitudes of 70- to 110-Hz frequencies and a decrease in the magnitudes of 10- to 30-Hz components during acute rejection (131). Subsequently, the 50- to 110-Hz/0- to 30-Hz area ratio was reported to detect rejection with 80% sensitivity and 77% specificity (132).

Recommendations for use of signal-averaged ECG. On the basis of the few studies available, the consensus of the committee is that the potential of signal-averaged ECG analysis to detect acute rejection of heart transplants is promising, but currently unproved. Further supportive evidence and refinements of methods of analysis are needed.

Clinical Utilization and Cost

As a general principle, diagnostic tests are most effective when utilized in patients with an intermediate pretest likelihood of the suspected condition. Conversely, the test is less indicated at extremes of pretest likelihood. The positive predictive value of signal-averaged ECG, like other tests, varies with antecedent risk. For instance, the risk of ventricular arrhythmia after myocardial infarction is reduced by prior thrombolytic therapy. Further, the relatively low positive predictive accuracy of signal-averaged ECG analysis as a stand-alone test indicates that it is also best used with other diagnostic methods. As shown in Table 5, the use of signal-

averaged ECG is considered in conjunction with the extent of left ventricular dysfunction, frequency and complexity of ventricular ectopic activity, heart rate variability and response to programmed ventricular stimulation. Results of the prospective studies cited have demonstrated that when the signal-averaged ECG is used in combination with other determinants of risk, the overall positive predictive accuracy may be as high as 50%.

The potential diagnostic value and cost of various combinations of diagnostic tests for sustained ventricular arrhythmia after myocardial infarction are summarized in Table 4 for single tests and in Table 5 for combined tests. The data illustrate the complexity of balancing diagnostic accuracy and cost.

The signal-averaged ECG is billed under CPT code 93278. Although this code has not been uniformly reimbursed by Medicare carriers across the United States, the number of studies that were reimbursed by Medicare increased from 33,796 in 1992 to 34,950 in 1994. Data from the private sector are currently unavailable. In Medicare in 1994, 76.2% of signal-averaged ECGs were billed by cardiovascular specialists, whereas 17.3% were performed by internists. The signal-averaged ECG was recorded predominantly in patients >75 years old (62.6%), most frequently in men (65.5%) and inpatients (54%).

In 1995, Medicare relative value units (RVU) for CPT code 93278 when billed as a global service totaled 2.18 (0.35 physician work, 1.65 overhead, 0.18 malpractice), providing an average nationwide reimbursement of $74.56. Smaller amounts are paid for interpretation alone or for only the technical component. Total estimated Medicare expenditures to cardiovascular specialists for this service of $1.5 million in 1994 may increase as this service becomes more uniformly covered by Medicare, as the indications become more widely known and as appropriate technology becomes more readily available at a reduced cost.

The use of signal-averaged ECG technology is a relatively modest component of total cardiovascular health care expenditures. Currently, expenditures for this code are a negligible percentage of both 1993 Part B Medicare physician expenditures, estimated at $35 billion, and cardiovascular specialist expenditures, estimated at $3.3 billion.

Refinement of Methods of Data Analysis

Current research is establishing the extent to which the terminal QRS complex and ST segment are optimal ECG intervals and orthogonal ECGs are the ideal leads for detecting signals generated by myocardial tissue responsible for sustained ventricular arrhythmias. Results of analysis of three-dimensional, computer-assisted, ventricular activation maps recorded during sustained ventricular tachycardia (11) and sinus rhythm (133) from patients with healed myocardial infarction undergoing arrhythmia surgery have shown that 1) both intramural macroreentry and focal mechanisms underlie sustained monomorphic ventricular tachycardia in humans with healed myocardial infarction; 2) current methods of signal-averaged ECG analysis limiting interrogation to the terminal QRS/ST segment exclude detection of >95% of the signals generated by myocardium responsible for sustained ventricular tachycardia; and 3) late potentials detected in signal-averaged ECGs correspond to delayed activation of epicardial sites that are temporally and spatially remote from the tissue responsible for ventricular tachycardia.

These findings provide an objective rationale for expansion of the ECG interval analyzed to include more of the cardiac cycle, which should increase the chances of detection of signals generated by myocardium critical to ventricular tachycardia. Indeed, previously undefined magnitude (134,135), phase (136) and spatial (137,138) features over the entire cardiac cycle of sinus beats that distinguish signal-averaged ECGs from patients with from those without sustained ventricular tachycardia have recently been identified.

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