DIAGNOSTIC METHODS

VENTRICULAR ARRHYTHMIA

Electrical alternans and cardiac electrical instability

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ABSTRACT We investigated the relationship between electrical alternans and cardiac electrical stability in a series of 20 dog experiments and in a pilot clinical study. Electrical alternans was detected in both the QRS complex and the ST-T wave by use of a novel multidimensional spectral technique. The magnitude of the alternation was expressed as the alternating electrocardiographic morphology index (AEMI), expressed as parts per million of waveform energy. Electrical stability in the dog preparations was assessed via the ventricular fibrillation threshold measurement, and in the clinical studies via programmed stimulation. In 10 dog experiments, systemic hypothermia resulted in a 60% decrease in ventricular fibrillation threshold (VFT) (p < .0001) and a significant increase in both AEMI(QRS) from 3.7 ± 3.0 to 1448 ± 548 (p < .0001) and AEMI(ST-T) from 43.9 ± 18.4 to 19,178 ± 5579 (p < .0001). In 10 dog experiments, transient coronary artery ligation also resulted in a 60% decrease in VFT (p < .0001), an increase from 76.3 ± 46.5 to 245 ± 11 in AEMI(QRS) (p < .05), and an increase from 842 ± 505 to 1365 ± 392 in AEMI(ST-T) (p < .002). In 119 observations in 20 animal experiments, the rank correlation between VFT and AEMI(QRS) was −.30 (p < .001), with that between VFT and AEMI(ST-T) being −.55 (p < .0001). In a double-blind pilot clinical trial consisting of 23 studies in 19 patients, the result of electrophysiologic testing was used as an independent measure of cardiac electrical stability. Alternation in waveform morphology identified the inducible patient population with a sensitivity of 92%, a positive predictivity of 70%, and a specificity of 50% (p < .05). We conclude that analysis of subtle beat-to-beat variability in electrocardiographic morphology may provide a noninvasive measure of cardiac electrical stability. Circulation 77, No. 1, 110–121, 1988.

IN THE LAST FEW YEARS, there has been great interest in the study of chaotic behavior in nonlinear systems. Particular interest has been focused on the description of system behavior during the transition from stable to chaotic regimes. One intriguing result has been the description of a “universal” period-doubling route to chaos, suggesting that a diverse set of complex dynamical systems approach their chaotic regimes through a universal pathway.1-3 The touchstones along this common route to chaos are period-doubling or subharmonic bifurcations. A system driven at a fixed frequency \( \omega \) begins to demonstrate excitations at subharmonics of the driving frequency as it approaches its chaotic regime, first \( \omega/2 \), then \( \omega/4 \), \( \omega/8 \), \( \omega/16 \), etc., until the system finally enters the aperiodic chaotic regime.

The spread of electrical excitation throughout the ventricular myocardium constitutes a complex, highly nonlinear physical process. This system is driven quasiperiodically by spontaneous electrical excitation, normally originating in the sinus node. The driving frequency is the heart rate itself. Electrical alternans may therefore be viewed as the first subharmonic bifurcation of this process, constituting an excitation at one-half of the driving frequency. Electrical alternans refers to variation in electrocardiographic (ECG) waveform morphology on an every-other-beat basis, i.e., an ABABA . . . pattern. In this context, electrical alternans might be interpreted as a marker that the system of cardiac electrical activation is approaching its chaotic regime, characterized by reentrant rhythm disturbances such as ventricular tachycardia and fibrillation.

Electrical alternation in ECG complex morphology may result from mechanical “flip-flopping” of the heart.
on a beat-to-beat basis, as occurs with pericardial effusion and tamponade.1-6 This form of electrical alternans is believed to result from mechanical movement of the heart within the pericardial sac, as opposed to a specific electrophysiologic abnormality. Electrical alternans has also been linked to prolonged QT syndromes,7-10 paroxysmal tachycardia,11-14 bradyarrhythmias,1,15 exercise testing,1,16,17 cardiovascular drug therapy,18,19 Wolff-Parkinson-White syndrome,20,21 various intoxications,22-24 electrolyte imbalances,22-27 hypothermia,28 coronary artery spasm,29-33 and coronary artery occlusion.28,34-38 Clinical observations have been made of increased incidence of electrical alternans and spontaneous ventricular fibrillation in patients with either of the prolonged QT syndromes7,8 and in patients with Prinzmetal’s angina.29,30,32,33 These observations suggest that electrical alternans may be caused by electrophysiologic alterations, and that this form of electrical alternans may be related to cardiac electrical instability. For the remainder of this discussion, we will focus on this form of primary electrical alternans as opposed to electrical alternans secondary to mechanical movement of the heart. As will be subsequently discussed, our methods of analysis are designed to minimize the effects of mechanical alternation resulting from beat-to-beat cardiac rotation.

Recent work in our laboratory has demonstrated that finite-element models of cardiac conduction processes display alternation in synthesized ECG waveforms as these models are made increasingly unstable.39,40 In these models, subpopulations of sites with prolonged refractory periods may respond to every other stimulation, leading to alternate patterns of excitation and recovery in successive beats, thus giving rise to macroscopically observable electrical alternans. These subpopulations provide evanescent barriers to conduction, which facilitate wavefront fractionation and reentry, thus linking the mechanisms of formation of electrical alternans and reentrant arrhythmogenesis.

The first quantitative study attempting to relate electrical alternans with myocardial electrical stability demonstrated that electrical alternans in vivo may be so subtle as to preclude visual detection, yet be statistically significant and easily measurable with digital signal processing techniques.28 That study was restricted to an examination of T wave alternans and focused on alternation in waveform energy, demonstrating that within a single experimental preparation, a relative increase in the amount of alternans detected was accompanied by a relative decrease in the measured ventricular fibrillation threshold (VFT).

Waveform energy, however, is a degenerate metric waveform morphology in the sense that an infinite number of waveforms may have the same energy. As a result, the study of waveform energy can be insensitive to morphologic variation if the overall energy of the waveform is largely unaffected. In extending that initial study, we have developed a nondegenerate multivariate spectral analysis procedure to quantify the degree and statistical significance of waveform alternation present in the magnitude of the three orthogonal–lead electrocardiogram, and have expanded the analysis to include both QRS and ST-T wave morphology. In this article we report on the relationship between electrical alternans and electrical stability in experimental models of both acute coronary artery ligation and systemic hypothermia. We also report on a preliminary clinical study probing the relationship between ECG waveform alternation and the results of immediately subsequent electrophysiologic (EP) testing.

Methods

Animal studies. Experimental studies were conducted under the supervision of the Division of Comparative Medicine at MIT, with preapproved protocols conforming to the NIH guidelines for animal experimentation. Twenty mongrel dogs, 15 to 25 kg in weight, were anesthetized with 1 mg/kg of acepromazine subcutaneously and 30 mg/kg of sodium pentobarbital (Nembutal) intravenously. Additional pentobarbital was given as needed to maintain deep anesthesia. Respiration with room air was maintained by means of an air-cuffed endotracheal tube connected to a mechanical ventilator. Arterial blood gas measurements were made at 45 to 90 min intervals (more frequently during rapid changes in core temperature). Respiration rates were adjusted to maintain systemic arterial Pco2 between 35 and 45 mm Hg (IL Blood Gas machine model 213/326), with Po2 never falling below 80 mm Hg. Three pairs of transcutaneous needle electrodes were applied along the three cardinal (orthogonal) directions (lateral limb lead, X; rostral-caudal lead, Y; dorsal-ventral lead, Z) for the recording of the three orthogonal–lead electrocardiogram (Electronics for Medicine ECG amplifier, bandpass 0.04 to 500 Hz). Systemic arterial pressure was monitored via an intra-arterial catheter connected to a Statham P23a transducer. The three ECG signals and the arterial pressure signal were recorded on a Hewlett-Packard 3968A eight-track FM instrumentation tape recorder with tape speed set to 3½ ips (3 dB bandwidth of 0 to 1250 Hz).

The surgical preparation for each of the experiments was begun with a left lateral thoracotomy. The pericardium of each dog was incised and the heart was suspended in a pericardial cradle. One pair of barb-type pacing electrodes (Medtronic model 4951) was applied to the left atrial appendage, and a second pair of sutureless screw-type electrodes (Medtronic model 6917A) was applied to the left ventricular free wall between the first and second diagonal branches of the left anterior descending coronary artery (LAD) (for VFT determination). The interelectrode distance was set to be approximately 2 cm, with both the anode and cathode placed within a conceptual watershed area between the first and second diagonal branches off the LAD, constituting a peri-ischemic or border zone area
in the case of LAD occlusion just distal to the first diagonal.

For the coronary occlusion studies, a 1 cm segment of the LAD just distal to the first diagonal branch was dissected free from the surrounding fascia, and an inflatable saline-filled vascular occlusion cuff (In Vivo Metric, Healdsburg, CA) was securely fastened around the artery. The pericardium was then loosely approximated, the muscle and skin layers were closed separately, and the chest was evacuated of air via a suction drainage tube. After a recovery period of 30 to 45 min, ECG and blood pressure recordings were made during atrial pacing. The minimum pacing rate was that required for reliable override capture of the spontaneous rate, and the maximum was the highest pacing rate yielding 1:1 conduction, up to a maximum of 200 beats/min. VFT determinations were made at the extremes of the range of pacing rates with repeat or successive VFT determinations separated by at least 15 min. Transient (10 min) coronary artery occlusions were then conducted at each of the same pacing rates. VFT measurements were made between the third and fifth minute of occlusion. In the event of spontaneous ventricular fibrillation, the VFT was taken to be zero.

In the hypothermia experiments, a thermocouple was sutured in place within the pericardium, and the pericardium and chest were closed as described above. In addition, a countercurrent heat exchanger was connected between the right femoral artery and the left femoral vein. After a recovery period of 30 to 45 min, ECG and blood pressure recordings were made at several atrial pacing rates, with VFT determinations again being made at the extremes of the range of pacing rates. The dogs were then anticoagulated (heparin, 100 μg/kg iv), and the femoral artery – femoral vein bypass heat exchanger was opened. The temperature of the countercurrent flow was regulated so that the target temperature of 29°C was reached in 90 to 120 min. At this temperature, the experimental protocol established under normothermic conditions was repeated as tolerated. Once data collection at hypothermic temperatures was completed, the temperature of the countercurrent flow was raised, with rewarmin to initial temperatures being accomplished in approximately 60 to 90 min. Data collection and VFT determinations were repeated at normothermic temperatures, and the animals were euthanized.

**VFT determinations.** The VFT was measured via the pulse train technique. A PDP 11/23 based 16-bit laboratory computer with a built-in digital-to-analog converter (Digital Equipment Corp., MINC — Declab) was used for generating the appropriate time delay, gating, and amplitude of the stimulus pulse train. This analog output was connected through an isolation amplifier to a voltage-to-current converter, the output of which was connected to the pair of ventricular electrodes. For these studies a 100 Hz pulse train with 50% duty cycle was applied through the pair of ventricular electrodes. The pulse train was gated so that it began in the mid QT segment and extended just beyond the T wave on the scalar electrocardiogram, thereby scanning the vulnerable period and the immediately adjacent protective zone. The amplitude of the current pulse train was initially set at 2 mA and increased in 2 mA increments every 10 paced beats until ventricular fibrillation was initiated. The minimum current intensity resulting in ventricular fibrillation was taken as the VFT.

**Methods of analysis.** The data analysis scheme is depicted in figure 1. After selection of the data segments to be analyzed, the ECG output channels from the Hewlett-Packard 3968A FM tape recorder were connected through six-pole Butterworth low-pass filters (cutoff frequency set to 360 Hz) to a Masscomp MC500 laboratory computer. The ECG channels were each digitized at a rate of 1 kHz, with 12-bit precision. QRS complexes were then identified and fiducial points were determined by a template-matching based QRS detection algorithm. The resulting annotations and RR intervals were then graphically examined for evidence of spurious and/or undetected events. The annotation file was subsequently edited to reflect only the locations of normal QRS complexes. Data segments containing ectopic depolarizations, skipped beats, or intermittent pacing capture were omitted from further analysis. After this initial phase of QRS complex detection, a second phase was initiated in which an iterative, adaptive template-matching (matched-filter) scheme was used to refine initial fiducial point estimates. For this refinement phase, the vector magnitude waveform of the QRS complex was calculated for each beat. This was done by calculating the square root of the sum of the squares of each of the three baseline-corrected orthogonal leads. Baseline correction included estimation of the baseline in the isoelectric PQ segment by averaging 16 successive samples in this time window for each lead and subsequently subtracting this estimate before

![Data analysis scheme for detecting alternation in waveform morphology.](http://circ.ahajournals.org/)

**FIGURE 1.** Data analysis scheme for detecting alternation in waveform morphology.
construction of the vector magnitude. The average vector magnitude QRS complex was then calculated with the use of initial fiducial point estimates to align each waveform. With this average as a template, the fiducial points corresponding to each QRS complex were then shifted to maximize the cross-correlation between each candidate beat and the template. The template was then recalculated with the use of refined fiducial point estimates, and the process was repeated until all fiducial points converged. Typically, convergence was established after only one pass of the refinement procedure.

Once fiducial points for all complexes stabilized, alternation in ECG complex morphology was quantified by a multidimensional spectral estimation technique. In brief, the vector magnitude ECG signal was analyzed by first delineating two adjacent and nonoverlapping intervals, one corresponding to depolarization events (a 100 msec window centered about the peak amplitude in the QRS vector magnitude), and one corresponding to repolarization events (a 200 msec window immediately after the depolarization window, corresponding to the ST segment and T wave). After the initial automated demarcation of these windows, a display of the superposition of all of the ECG epochs relative to these two windows was used to ensure that the QRS window included the entire time course of depolarization.

Thus, for a sequence of $N$ successive ECG epochs ($N = 128$), two data matrices were constructed, $\text{QRS}(n,m)$ and $\text{STT}(n,m)$, where $n$ is the index over successive beats and $m$ is the index over successive samples within the same beat. The QRS data matrix thus consisted of 128 rows (each corresponding to a successive QRS complex) and 100 columns (each column corresponding to a one sample point during the QRS). The ST-T wave data matrix similarly had 128 rows, each corresponding to successive ST-T waves, and 100 columns, here representing every other sample of the original ST-T waves. (For the fastest atrial pacing rates, the ST-T wave interval was truncated just before the onset of the earliest atrial pacing spike to avoid the confounding influence of beat-to-beat variability in pacing spike location. This would infrequently occur as a result of beat-to-beat variability in stimulus latency or atrioventricular conduction time.) Alternation in ECG morphology would then be reflected as alternation in the sample values looking down the columns of the data matrix. However, the effects of electrical noise, respiratory modulation of ECG morphology, muscle artifact, etc., would tend to obscure this alternation. Frequency spectral decomposition allows for detection and separation of frequency specific components (such as alternation in morphology) in the presence of such noise sources.

For this reason, each column in each of the data matrices was subjected to power spectral estimation via calculation of the discrete Fourier transform of the Hanning-windowed sample autocorrelation function. These estimates were then algebraically summed over all of the columns, thus generating one power spectrum for each of the two data matrices. Examples of the ECG tracings and the associated power spectra are shown in figure 2.

The point in the aggregate power spectrum corresponding to alternation was compared with an estimate of the noise in an adjacent spectral band by construction of the sample mean and sample standard deviation of eight frequency samples in that band. Alternation in morphology was judged significant if the power at the frequency of alternation exceeded the estimate of the noise mean by three standard deviations. The value reported for the amount of alternation present was the amount by which the power at the alternans frequency exceeded the mean noise power estimate, normalized by the energy of the average waveform. For the QRS complex, this was reported as the alternating ECG morphology index (AEMI) for the QRS, denoted $\text{AEMI}(\text{QRS})$. For the ST-T wave, this was denoted AEMI (ST-T).

**Clinical study.** All patients in this study gave informed consent for both the recording of the ECG data and for the standard EP testing protocol. For the duration of the study enrollment consisted of all consenting patients referred for EP study, without regard to the specific reason for study or preceding clinical history. Electrocardiographic data in the form of three orthogonal lead projections (either the Frank lead system or leads I, aVF, and V_{1,2}) were recorded from each of 19 adult patients immediately before EP testing. (See table 1 for details on the patient population.) One patient was studied on three separate occasions, and two others were studied twice, thus providing 23 recording sets in all. The recorded data included 2½ min of ventricular pacing at each of three different rates (100, 120, and 150 beats/min). The three channels of data were initially recorded on a Teac 14-channel FM tape recorder at a tape speed of 15 ips, corresponding to a 3 dB bandwidth of 625 Hz, and were later rerecorded on an HP 3968A eight-channel tape recorder (tape speed of 3⅓ ips, corresponding to a 3 dB bandwidth of 0 to 1250 Hz) for subsequent analysis.

Results of off-line analysis were compared to the results of the EP stimulation protocol. Patients were divided into two groups according to whether sustained ventricular tachycardia could be

![FIGURE 2. The three orthogonal ECG tracings (X, Y, and Z) during transient coronary artery ligation are shown in A. Careful inspection of the traces reveals alternation in ST-T wave morphology. B. The power spectrum of the morphologic variation in QRS morphology. The dominant peak in the spectrum (at a relative frequency of 0.1 cycles/beat) is due to respiratory modulation of QRS amplitude. C. The same plot, now for ST-T wave variation. Respiratory modulation is again present and the subtle alternation is now easily detected.](http://circ.ahajournals.org/attach/circ/circ1.1411769806.2964882/1551161.1551162/P1582656334193-038434216.pdf?Expires=1510414305&OAccessKeyId=95E0N0B1K4G0QW reactions4QV0xRQ1&Signature=10OZ5dE%52HbTF%KQy2p0Mo5%2945K2h%3D)](http://circ.ahajournals.org/attach/circ/circ1.1411769806.2964882/1551161.1551162/P1582656334193-038434216.pdf?Expires=1510414305&OAccessKeyId=95E0N0B1K4G0QW reactions4QV0xRQ1&Signature=10OZ5dE%52HbTF%KQy2p0Mo5%2945K2h%3D)
induced in a standard EP testing protocol (for details of the testing protocol, see Ruskin et al.44).

**Patient population.** The 19 patients included 17 men and 2 women. Ages ranged between 32 and 74 years, with a mean age of 58 years. Among the 19, 16 had received a primary diagnosis of atherosclerotic heart disease (ASHD); 15 of these had documented previous myocardial infarctions. Of the remaining three, one had no structural heart disease (normal cardiac catheterization), one had idiopathic hypertrophic subaortic stenosis (IHSS), and the third had idiopathic cardiomyopathy (CM). Nine patients had suffered cardiac arrests; eight of these had ASHD and one had IHSS.

**Method of analysis.** The method of analysis of these data differed from that used in the animal studies only in the particulars of the data windows corresponding to the QRS and ST-T wave segments. In the animal studies, the window corresponding to depolarization was taken to be 100 msec centered about the middle of the vector magnitude QRS complex. In the human studies, this window was extended to be 150 msec wide to encompass the wider QRS complexes resulting from ventricular pacing. Similarly, the window corresponding to repolarization (ST-T) was taken to be 225 msec wide as compared with 200 msec for the animal data. The resultant data matrices each consisted of 75 rows; for the QRS complex each row corresponded to every other sample of the original waveform, and for the ST-T wave each sample corresponded to every third sample or the original waveform. All remaining data analysis was the same as in the animal studies.

**Statistical methods.** Due to the obviously nonnormal distribution of both the VFT and the AEMI data, nonparametric statistics were used to test for significance of results. In particular, the sign test was used to test for significance of changes in VFT and AEMI within a set of matched data point pairs, and correlation between the AEMI values and the VFT values was tested via the rank correlation test. The Wilcoxon rank-sum test was used to test for a significant difference between the AEMI values in the inducible vs noninducible populations. The contingency table of results from the clinical study was subjected to the chi-square test for statistical significance.

**Results**

**Animal studies.** Ten dogs were subjected to hypothermia (lowering of their core temperature to 29°C from the control temperature of 35 to 37°C). Figure 3 illustrates the ECG waveforms under normothermic and hypothermic conditions, providing an obvious example of alternation in ECG morphology that accompanies hypothermia. In seven of these experiments, two sets of measurements were made (at pacing rates dif-

### TABLE 1
Clinical data base used for comparing outcome for electrophysiologic testing with detection of alternation in ECG complex morphology

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<th>Study</th>
<th>Age (yr)</th>
<th>Sex</th>
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<th>Arrest</th>
<th>EP result</th>
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The last column denotes presence or absence of electrical alternans, with an indication of whether alternans was detected in QRS, ST-T, both, or neither.

RFS = reason for study; ASHD = atherosclerotic heart disease; NSHSD = no structural heart disease; CM = cardiomyopathy; IHSS = idiopathic hypertrophic subaortic stenosis; VPA = ventricular ectopic activity; CHD = congenital heart disease; SUSVT = sustained ventricular tachycardia; NSVT = nonsustained ventricular tachycardia; NI = not inducible; VF = ventricular fibrillation.
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FIGURE 3. ECG leads X, Y, and Z under normothermic and hypothermic conditions. At 37°C, with a VFT of 14 mA, no alternation is appreciated, either visually or via spectral analysis. At 29°C, 1 min before spontaneous ventricular fibrillation, frank alternation is observable on QRS peak amplitude and ST-T wave morphology (lead Y, middle trace).

Ten dogs were subjected to transient occlusion of the LAD. Figure 6 depicts the time course of both AEMI(QRS) and AEMI(ST-T) during transient coronary artery ligation in one experiment. Figure 7 illustrates the combined effect of pacing rate and coronary artery ligation on AEMI(QRS) and AEMI(ST-T) and VFT in a separate experiment. Over the series of 10 experiments, 24 different measurement sets were obtained. Coronary artery occlusion was accompanied by a decrease in VFT in all of the 24 measurement sets, from a preocclusion value of 23.0 ± 2.4 mA to a value of 7.8 ± 1.6 mA in the occluded state (p < .0001). On average, coronary artery occlusion reduced the measured VFT by 61%. Occlusion was accompanied by an increase in AEMI(QRS) in 10 of the 24 measurement sets and a decrease in AEMI(QRS) in three of the 24 sets, but QRS alternans was undetectable in both recordings in 11 of the 24 sets (p < .05). The average preocclusion value for AEMI(QRS) was 76.3 ± 46.5 ppm and that during occlusion was 245 ± 111 ppm

Reducing by at least 25 beats/min from each other), while in the remaining three experiments, only one set of measurements could be made. As determined from the 17 sets of measurements, hypothermia reduced VFT in all experiments, from a normothermic value of 23.8 ± 2.5 mA (mean ± SEM) to a hypothermic value of 8.5 ± 1.0 mA (p < .0001). On average, hypothermia reduced the measured VFT by 61%. AEMI(QRS) increased in 16 of the 17 measurement sets as a result of hypothermia, and remained unchanged (with alternans undetectable) in the remaining measurement set (p < .0001). The average AEMI(QRS) under normothermic conditions was 3.7 ± 3.0 ppm (parts per million of waveform energy), and under hypothermia it was 1488 ± 548 ppm. AEMI(ST-T) was found to increase in all 17 of the measurement sets as a result of hypothermia, from a normothermic value of 43.9 ± 18.4 ppm to a hypothermic value of 19,178 ± 5,579 ppm (p < .0001). Figure 4 illustrates the relationship between AEMI(QRS) and AEMI(ST-T) and pacing rate for two different core temperatures. In the hypothermic case, alternating activity increased with increasing pacing rate, until spontaneous ventricular fibrillation intervened at a rate of 190 beats/min. In the normothermic control, no alternans was seen, regardless of pacing rate. Figure 5 illustrates the relationship between VFT and AEMI(ST-T) for all measurement sets.
FIGURE 4. The relationship between AEMI(QRS) and AEMI(ST-T) and atrial pacing rate in hypothermia vs control. In the control preparation, alternans is undetected, independent of pacing rate. With hypothermia, electrical alternans is seen in both QRS and ST-T waves, and the relative magnitude increases with pacing rate. Spontaneous ventricular fibrillation intervened at a pacing rate of 190 beats/min.

ppm. AEMI(ST-T) was found to increase in 17 of the 24 measurement sets and it decreased in three of the 24 sets, with ST-T alternans being undetected in four of the sets (p < .002). The preocclusion average value for AEMI(ST-T) was 842 ± 505 ppm, and the average during occlusion was 1365 ± 392 ppm.

In total, 119 pairs of measurements (VFT and AEMI) were made in this set of animal experiments. The rank correlation coefficient between VFT and AEMI(QRS) was −.30 (p < .001). The rank correlation coefficient between VFT and AEMI(ST-T) was −.55 (p < .0001) (see figure 8).

FIGURE 5. The relationship between VFT and AEMI(ST-T) as a result of systemic hypothermia. The open circles represent the normothermic control state and the closed circles represent the hypothermic state. Hypothermia is associated with a decrease in VFT and an increase in alternation of ECG morphology.

FIGURE 6. Time course of the development of ECG waveform alternation with coronary occlusion. Alternation accompanies coronary artery ligation, appears transiently increased with reperfusion, then disappears after 2 min of reperfusion.

Clinical trial. A description of the patient population and results are provided in table 1. In the clinical study, alternation was considered to be detected if significant (three standard deviations above the noise floor) alternation was detected at any of the three pacing rates. Of the 23 recordings, 17 were found to have significant
inducible group was 1571 ± 1091 ppm (mean ± SEM) and that for the noninducible group was 362 ± 192 ppm (NS).

A standard 2 × 2 contingency table was constructed to determine whether alternation of ECG morphology was a significant discriminator in identifying patients in whom ventricular tachycardia or fibrillation was inducible (figure 9). The presence of alternation in either QRS complex or ST-T wave (considered together) served as a statistically significant discriminator for this purpose. When considered separately, neither QRS nor ST-T alternants alone was sufficient for this purpose. Detection of electrical alternans in either waveform segment identified the “inducible” patient population with a sensitivity of 92%, a specificity of 50%, and a positive predictivity of 70% (p < .05). Only one of the 13 patients in whom tachycardia/fibrillation was inducible was not identified by this technique.

**Discussion**

In the series of animal experiments, we set out to address the question of whether alternation of ECG morphology might serve as an ECG indicator of cardiac stability, with the use of hypothermia and coronary artery occlusion as destabilizing interventions. We found that hypothermia was uniformly accompanied by a decrease in electrical stability (as documented via VFT measurement), and that the ECG vector magnitude during hypothermia revealed alternating morphology both in the QRS complex and in the ST-T wave. In these experiments, a decrease in VFT was always accompanied by an increase in ST-T alternants, and was accompanied by an increase in QRS alternans in 16 of 17 cases. In the one remaining case, QRS alternans was not detected either in the control or the hypothermic setting. In general, ST-T alternans during hypothermia was much larger in magnitude than QRS alternans.

We found that coronary artery occlusion was also uniformly accompanied by a decrease in electrical stability (as measured by the VFT) and that occlusion was frequently accompanied by an increase in the observed alternation in ECG vector morphology. In contrast to the hypothermia studies, with coronary artery ligation a decrease in VFT was not always accompanied by detectable electrical alternans, and there was an obvious difference in the relative incidence of QRS and ST-T alternans. In 11 of 24 cases, QRS alternans was undetectable both before and after coronary artery ligation. In four of the 24, ST-T alternans was similarly undetectable. Of those cases in which electrical alternans was detected, however, the relationship between

**FIGURE 9.** The 2 × 2 contingency table illustrating the use of detected alternation in ECG waveform morphology as a discriminator for predicting inducibility of ventricular tachycardia or ventricular fibrillation during electrophysiologic testing.
electrical alternans and VFT was clear, with 10 of 13 cases showing increasing QRS alternans and 17 of 20 cases showing increasing ST-T alternans as VFT decreased.

This study does not provide a direct explanation for the observed differences between results of the hypothermia and coronary artery ligation studies, but we may speculate that hypothermia as an intervention affects the entire myocardium, whereas coronary artery ligation has a very regional effect. The amount of alternation seen in the electrocardiogram is undoubtedly related to the mass of myocardium undergoing local alternation in activation/recovery processes, and thus a higher incidence of detectable electrical alternans in the hypothermia experiments is not unexpected.

Detection of alternans is based on a statistical technique, and as such, ambient electrical noise, muscle artifact, etc., may obscure subtle alternation in morphology in either or both waveform segments. Also, body surface potentials reflect a degenerate representation of the electrical activity of the heart. Thus, in generating body surface potentials, alternating activity at different locations within the heart may add constructively at some times and destructively at others, depending on the spatial relationship of the different regions and on the temporal relationship of the activation/recovery sequences. In these experiments, postintervention ST-T alternans was generally more pronounced than postintervention QRS alternans. Alternation in repolarization processes may be the primary event that leads to QRS alternans only when the time between successive beats is sufficiently short such that incomplete recovery significantly alters the pattern of subsequent activation. In those very few instances in the coronary occlusion study and in the clinical study in which we detected QRS alternans in the absence of ST-T alternans, we hypothesize that repolarization alternans may have been present, but it was not detected as ST-T alternans in the surface vectorcardiogram as a result of measurement limitations.

While a systematic study of the effect of pacing rate on the relationship between electrical alternans and electrical stability is not presented in this series of experiments, in an earlier study we demonstrated that an increase in atrial pacing rate from 140 to 200 beats/min was associated with a decrease in VFT and an increase in the amount of electrical alternans measured. In the present series, we noted that under conditions of hypothermia and coronary artery occlusion increased pacing rates were associated with diminished electrical stability and increased electrical alternans. Figure 4 illustrates the effect of pacing rate on observed electrical alternans in hypothermia and in the normothermic control. Alternans increased with pacing rate until spontaneous ventricular fibrillation intervened at a pacing rate of 190 beats/min. Figure 7 illustrates that in the case of coronary artery occlusion, more rapid atrial pacing rates were also associated with greater alternation in ECG morphology and lower VFTs.

Figure 5 demonstrates that relative changes in stability are accompanied by relative changes in the amount of alternation present in waveform morphology within a single preparation. A stronger statement is made by the rank correlation of all VFT measurements with the associated AEMI measurements. The finding of significant (negative) correlations between VFT measurements and both QRS and ST-T wave alternation metrics across the entire set of measurements demonstrates a relationship between the absolute amount of electrical alternans detected and the absolute value of the VFT, suggesting that the quantitative measure of alternation in ECG morphology may be an index of cardiac electrical stability. This relationship prompted a small pilot clinical study to determine the relative incidence of alternating ECG activity, and to provide an initial clinical test of the potential utility of this approach in identifying a patient population with diminished cardiac electrical stability (as measured by an independent technique, here by EP testing).

Of the 23 studies in 19 patients included in the clinical trial, 13 studies resulted in an induced tachyarrhythmia and 10 did not. The average AEMI(QRS) and AEMI(ST-T) values were larger in the inducible group than in the noninducible group, but the spread of the values precluded statistically significant separation of the two patient populations on this basis. Of the 13 studies in which tachyarrhythmias were induced, 12 corresponded to ECG data having statistically significant alternation present in either QRS or ST-T wave morphology. Of the 10 studies in which tachyarrhythmias were not induced, five were found to correspond to statistically significant alternation of either QRS or ST-T wave, and five corresponded to a lack of significant alternation. Alternation in either QRS or ST-T wave morphology identified the inducible group with a sensitivity of 92%, a specificity of 50%, and a positive predictivity of 70% (p < .05). As an intriguing aside, studies 17, 18, and 19, conducted on the same patient during the course of evaluation of antiarrhythmic therapy, demonstrated that alternans was detectable immediately before the two studies with positive results (tachycardia induced), but no alternans was detectable immediately before a negative result (tachy-
cardia not induced). In this one patient, the presence or absence of alternans seemed to predict the result of subsequent EP testing. This initial clinical trial suggests that electrical alternans exists in a more subtle form than previously appreciated, and that electrical alternation may be more prevalent than previously suspected, especially in the high-risk patients referred for EP testing. The results of this pilot study suggest that the presence of electrical alternans may indicate increased susceptibility to inducible rhythm disturbances.

It is important to note that this patient population was enriched in that each patient had some indication for EP study. As such there were no “normal” controls, and those patients in whom sustained arrhythmias were not inducible may not constitute an electrically stable group. In light of this, it is difficult to interpret data from the group of patients with detectable electrical alternans in whom tachycardia was not inducible, but who had histories of recurrent sustained ventricular arrhythmias. A much larger prospective study in which both EP testing and long-term follow-up will be used is being planned to assess the clinical utility of this approach in identifying the patient population at risk for malignant reentrant arrhythmias.

While this report demonstrates a relationship between electrical alternans and metrics of myocardial electrical stability, it does not directly address the mechanisms underlying such a relationship. Aside from mechanical causes of electrical alternans, such as beat-to-beat cardiac motion in the setting of pericardial effusion and pericardial tamponade,4-6 electrical alternans has been hypothesized to result from regions of myocardium with prolonged refractory periods, with individual regions responding on alternate beats, leading to alternation in the patterns of electrical activation and recovery. We have previously demonstrated that this hypothesis is sufficient to account for the observed relationship between electrical alternans and susceptibility to reentrant arrhythmias.39, 40 Alteration of action potential morphologies is a separate possible cause for the observed electrical alternans. Alternation of each of the four phases of the cardiac action potential has been previously reported.45 Recent unipolar mapping studies have suggested that electrical alternans accompanying ischemia may be the result of alternation in action potential morphology.46

Since we were interested in studying electrical alternans resulting from electrical events, we designed our experiments to minimize the effect of physical motion of the heart. We focused our attention on the study of fluctuations in the magnitude of the three orthogonal-lead electrocardiogram. The magnitude of the vectorcardiogram is independent of its specific orientation, and thus, to a first approximation, the magnitude waveform is insensitive to rotation of the cardiac structures on a beat-to-beat basis. However, there may be additional mechanical factors that may result in alternation of observed ECG morphology, serving as potentially confounding influences. Alternation in end-diastolic filling volumes would be expected to create some degree of electrical alternans on the surface electrocardiogram. Both the alternating source distributions (resulting from alternation in the conformation of the heart) and the alternating impedance field (resulting from the beat-to-beat alternation in the amount and distribution of blood within the thorax) could contribute to electrical alternans from a mechanical origin. Alternating atrioventricular nodal conduction times could result in alternating ventricular end-diastolic volumes, and thus might contribute to subtle alternation in ECG morphology via this mechanism. Also, alternation in atrioventricular nodal conduction times could result in electrical alternans based on the superposition of atrial repolarization with ventricular depolarization. Further work is needed to characterize the mechanisms and relative contributions of the potentially confounding sources of electrical alternans on the surface electrocardiogram. We note that the expected overall effect of these factors would be to diminish the observed relationship between electrical alternans and electrical stability. Continuous sonomicrometric measurements and beat-to-beat measurements of diastolic and systolic pressures and atrioventricular node conduction times will help delineate the relative impact of each of these confounding factors on our observations, further clarifying the relationship between primary electrical alternans and electrical stability.

While delineation of the specific cause or causes of the electrical alternans awaits more detailed analysis, the relationship between the measured alternation and the metrics of electrical stability is intriguing. Finite-element studies have suggested that electrical alternation is a natural marker for the destabilizing influence of a dispersion of refractoriness. In this framework, subpopulations of sites with prolonged refractory times, responding only to every other excitation wavefront, give rise to macroscopic electrical alternans and also provide the evanescent barriers to conduction that cause wavefront fractionation and reentry.39, 40 An entirely different perspective suggests that electrical alternans may represent the first of an infinite series of period-doubling bifurcations en route to chaos, but verification of this cannot be extrapolated from this
study. Chaos theory suggests that the first period-doubling bifurcation is the one most easily and frequently observed, because it occurs over the widest range of system parameters. Successive bifurcations occur over ever-diminishing ranges of system parameters, potentially complicating experimental observations of the higher order bifurcations. Alternately, the system of cardiac electrical activation may not follow the "universal" period-doubling route to chaos, and the electrical alternation that we observed may not be completely analogous to the first period-doubling bifurcation of chaos theory. Indeed, an initial experimental report and simulation studies on models of cardiac conduction processes have both observed that the system of cardiac conduction may display higher order periodicities that do not appear to follow the classic system bifurcation theory. New or amended forms of chaos theory may be needed to describe the stability of the system of cardiac electrical activation and the process of transition from normal, stable sinus rhythm to the cardiac chaos of ventricular fibrillation.

Our experimental and clinical observations demonstrating a relationship between electrical alternans and cardiac electrical stability are consistent with predictions made by finite-element models of cardiac conduction processes and with predictions based in part on nonlinear dynamics. We conclude that quantitative modeling of the complex determinants of cardiac conduction processes, together with developments in nonlinear systems dynamics, may provide useful insights into the behavior of the system of cardiac electrical excitation, and that statistical analysis of subtle beat-to-beat variability in ECG morphology may provide a noninvasive measure of cardiac electrical stability.

References
32. Rozanski JJ, Kleinfeld M: Alternans of the ST segment and T wave — a sign of electrical instability in Prinzmetal’s angina. PACE 5: 359, 1982
38. Russell DC, Smith HJ, Oliver MF: Transmembrane potential changes and ventricular fibrillation during repetitive myocardial ischaemia in the dog. Br Heart J 42: 88, 1979
43. Moody GB: ARISTOTLE: ambulatory real-time interactive system for testing on two-lead ECGs. MIT Bioengin Center, May 30, 1983