

Ventricular Fibrillation
and
Fluctuations in the T-wave

by

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ABSTRACT

Ventricular vulnerability to fibrillation has been related to the degree of spatial inhomogeneity of refractoriness in the myocardium. We studied the pattern of beat to beat fluctuations in the electrocardiogram T-wave in an effort to find a relationship between the time-varying components of ventricular repolarization and the Ventricular Fibrillation Threshold (VFT). Experiments were performed on dogs to reduce the VFT by means of hypothermia, tachycardia, and coronary artery ligation. All three interventions showed a characteristic pattern of alternans in the pattern of T-wave morphology fluctuations. The degree of alternans was quantified by the T-wave Alternans Index (TWA_I). We believe that the study of T-wave fluctuations can provide a useful noninvasive technique for the assessment of cardiac susceptibility to fibrillation.

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INTRODUCTION

Sudden Cardiac Death, defined as death resulting from cardiac origins within 24 hours of onset of symptoms, has been referred to as the most challenging problem facing contemporary cardiology. More often than not, SCD constitutes the first "symptom" of cardiac disease in an otherwise healthy individual, with over 25% of SCD victims having no prior recognized symptoms of heart disease ¹. In this country alone SCD claims over 1200 lives daily (about one each minute) each year, and represents the major cause of death in men between the ages of 20 and 64 ². Studies have shown that coronary artery disease is responsible for 90 % of the deaths attributed to sudden cardiac failure ³. It should be noted that Sudden Cardiac Death is not usually caused by acute myocardial infarction ⁴. It is thought that the mechanism responsible for the great majority of sudden cardiac deaths is ventricular fibrillation, a state in which the normally organized electrical activity of the heart becomes disorganized and chaotic. The chaotic electrical activity initiates disorganized and ineffectual mechanical contraction of the pumping chambers of the heart resulting in circulatory collapse and death.

Treatment of ventricular fibrillation is usually only a viable option for in-hospital episodes, but teams of specially trained rapid response personnel trained in emergency techniques have shown to make a significant contribution to patient survival rates following episodes of sudden death ⁵. In the overwhelming majority of out of hospital episodes, death occurs before adequate therapy can be initiated (Death will occur after about fifteen minutes of uninterrupted ventricular

fibrillation.) By far the more desirable and potentially the more effective response to this problem is prevention, in which the first step would necessarily be the identification of those individuals at an increased risk.

In that SCD is often the first presentation of severe cardiac disease, identification of those at risk is understandably a difficult problem. In those individuals with some prior cardiac symptomology, the problem is only marginally less difficult in that a great percentage of the adult population suffers from some cardiac ailment, yet relatively few of those individuals die suddenly. Despite the obvious difficulties, contemporary medical science has made some inroads into this problem.

By appealing to epidemiology, it is possible to determine statistical correlations between instances of SCD and various environmental and behavioral factors. These correlations can then be reduced to a list of risk factors, and by comparing an individual's behavioral traits, diet, level of physical activity, medical history, family medical history, etc. to a set of global risk factors, an assessment can be made as to the relative likelihood of an individual dying from SCD. This type of identification scheme alone suffers from a lack of both specificity and selectivity. Those individuals who are likely to die from SCD do not appear to be neatly separated from the rest of the population in terms of obvious demographic characteristics.

Several reports, most notably those by Reichenbach, Moss, and Vismara, ^{4,6,7} have said that the most important risk factor for sudden cardiac death is a history of previous myocardial infarction of signifi-

cant severity, with resulting impairment of cardiac function. Bernard Lown in 1971 proposed to identify those at risk of Sudden Cardiac Death by studying the incidence of ventricular premature beats (VPBs). By grading VPBs according to frequency, persistence, multiformity, repetitive pattern, and degree of prematurity, he has identified a group of patients with enhanced risk of sudden cardiac death as those with frequent advanced grades or complex forms of ventricular premature contractions⁸.

In hopes of gaining specificity and sensitivity, attempts have been made to directly or indirectly assess the cardiac status of a given individual. Electrocardiographic, echocardiographic, hemodynamic factors, and infrequently radiographic information are combined to arrive at a determination of an individual's cardiac health. The most recent and potentially most accurate procedure for assessing an individual's risk for SCD is electrophysiologic testing. In this form of testing, the patient is subjected to stressful exercise in an effort to provoke potentially threatening arrhythmias. In this manner, a quantitative measure of the heart's threshold to ventricular arrhythmias is obtained. However, electrophysiological testing is impractical to use as a generalized screening procedure because it is costly, time consuming, and has a demonstrated mortality rate that would be inconsistent with widely prescribed use.

Whereas electrophysiological testing is costly, time consuming, and is an invasive test (that is, the body's integrity is not maintained), the aim of this project has been to develop and test a system for determining susceptibility to sudden cardiac death in a manner that is non-

invasive, quickly obtained, and uses the standard ECG test leads as its input medium. This paper will concern itself primarily with the testing of such system, which showed a correlation between susceptibility to ventricular fibrillation as measured by the ventricular fibrillation threshold, and the temporal fluctuations in the morphology of the ventricular repolarization wave (T-wave) of the electrocardiogram.

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CARDIAC ELECTROPHYSIOLOGY

In order to understand cardiac dysrhythmias, it is first necessary to have a basic understanding of normal cellular electrophysiology, then to apply known principles to abnormalities thought to be the origins of dysrhythmias. Electrophysiology has its roots in the electrochemical energy of cellular function based on the creation of potential gradients across cell membranes. Such gradients result from the unequal distribution of ions (sodium, potassium, and calcium in particular) between the interior and the exterior of cells, and underlie the fundamental cardiac electrophysiological functions of automaticity (the initiation of cardiac impulses) and conduction (the propagation of such impulses). Electrochemical gradients and ionic movements among intracellular compartments relate primarily to metabolic and contractile functions.

In common with other cells, cardiac cells contain a relatively high concentration of potassium and protein ions with respect to the extracellular fluid⁹. However, they contain much less sodium, chloride, and calcium than a typical cell. This unequal distribution of ions results in part from differences in cellular permeability to the specific ions. The membrane is far more permeable to potassium than either sodium or calcium in the resting state¹⁰.

The cell membrane is continuously in a state of active transport of certain ions against electrochemical gradients. Energy dependent ion pumps transport sodium to the exterior and potassium to the interior of the cell¹¹. The transmembrane potential is determined by the transmem-

brane concentration gradients of various ions, and their relative permeabilities with respect to the membrane. Since the potassium ion is much more permeable in the resting state than the intracellular anions or extracellular cations, excess potassium will migrate down its concentration gradient from the interior to the exterior of the cell, without a reciprocal action of neutralizing charges. Thus, a negative resting potential results across the cell membrane. The typical value of such membrane polarization is -90 mV.

Following an appropriate excitatory stimulus to the myocardium, a transmembrane action potential results. The action potential is characterized by a large and rapid increase in membrane permeability to sodium¹². A representative cardiac action potential is shown in Figure 1. The rapid depolarization of the membrane represents a change in membrane characteristics from that of high permeability to that of high sodium permeability.

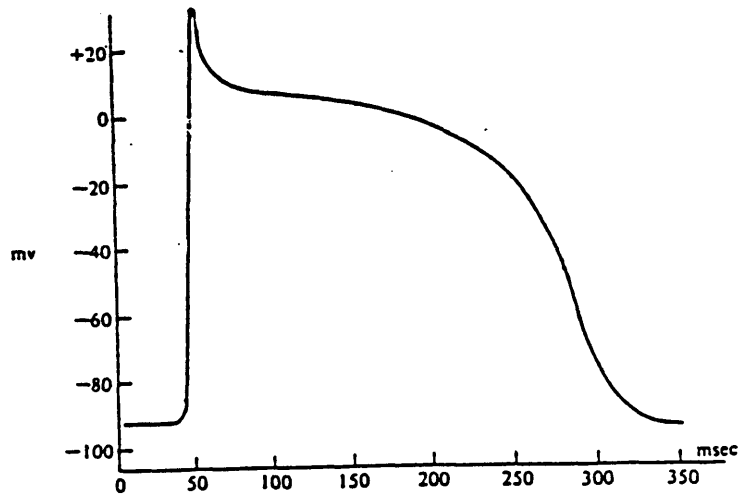


Figure 1.
A typical cardiac action potential

The permeability of the cell membrane to sodium ions depends upon the transmembrane potentials¹³. As the membrane partially depolarize (the result of electrical current outflow from neighboring myocardial cells) the permeability to sodium increases toward a threshold potential of approximately -60 mV. At the threshold, the membrane potential actively shifts from a state of potassium equilibrium to a state seeking sodium ion equilibrium. The driving force of this change is twofold: positive sodium ions are attracted to the interior of the cell by the negative intracellular potential, and the intracellular concentration of sodium is lower, resulting in a concentration gradient. The movement of sodium ions is rapid and large, resulting in an electrochemical overshoot (hyperpolarization) of nearly 25 mV as the cell strives to achieve sodium equilibrium.

At the end of the upstroke, the membrane permeability to sodium diminishes to a level consistent with that in the resting state; however, membrane potential does not immediately return to the resting level. Instead, it remains at a plateau near 0 mV for a period prior to repolarization. An important ionic feature of this plateau is the increased membrane permeability to calcium, which first manifests during the latter part of the upstroke and persists for a much longer duration than the transient increase in sodium permeability. Similar to the sodium channel, the calcium channel permits an inflow of positive ions to the cell.

The plateau is very important electrophysiologically because it delays the repolarization of the membrane and return to the resting

state. Because the cell cannot be excited again until it has repolarized to a level below that of the threshold, the plateau represents a refractory period, a time of cellular inexcitability following an excitation. Eventually, membrane repolarization occurs, the result of increases in the membrane permeability to potassium with corresponding decreases in the transient permeabilities to sodium and calcium.

While the majority of myocardial cells will remain at resting potential indefinitely in the absence of excitation, certain cells will undergo a gradual diastolic depolarization toward the threshold level. These cells are said to display automaticity. The cells that normally display automaticity are found in the sinoatrial (SA) node, certain regions of the atria, regions near the ostia of the coronary sinus, the atrioventricular (AV) node, the bundles of His, and the bundle branches¹⁴. Diastolic depolarization may have different mechanisms in different autonomic cells. In the SA node, where excitation normally originates, it is thought that diastolic depolarization is the result of a relatively high resting permeability to calcium, resulting in a voltage drift toward calcium equilibrium¹⁵.

Upon the generation of an action potential from autonomic foci, a flow of electrical current results in the depolarization of adjacent membrane, in turn producing additional action potentials. Thus, propagation of action potentials is achieved. Spatial continuation of the depolarization process is termed impulse conduction.

Several factors can influence the velocity of conduction: 1) the

action potential itself, particularly the level off the upstroke overshoot, which provides the voltage for excitatory current flowing across resting cell membranes. The greater the magnitude of the voltage (the greater the overshoot), the more current will flow and the sooner maximum levels of current will be obtained; 2) the upstroke rate, determined by the quantity of ionic flow across the membrane; and 3) the resistance of the cellular membrane to electron flow, which if low allows more current to flow ¹⁶.

The electrical currents generated in extracellular fluid during conduction are accompanied by gradients of electrical potential which can be observed. Potentials recorded in the vicinity of the heart at the body surface are referred to as electrocardiograms.

Once excited, the cardiac membrane undergoes a period of total inexcitability (the absolute refractory period) and a period of reduced responsiveness to stimulus immediately following (the relative refractory period) ¹⁷. Stimulus current greater than that under resting conditions must be applied to elicit response from the cell, and the upstroke of the action potential has a reduced overshoot and velocity. As a result, if tissue is excited during the relative refractory phase, conduction is slower than normal.

In normal myocardial cells, refractoriness is a function of membrane potential during repolarization. The absolute refractory period correspond to the time when the membrane is repolarizing above the level of the threshold. The relative refractory period is loosely

defined as the period that follows when the transmembrane potential is between the threshold and resting potentials. Of interest in this project is the concept of a vulnerable period, which falls somewhere within the relative refractory period. During the vulnerable periods, a stimulus of sufficient strength can initiate ventricular fibrillation. The vulnerable period occurs near the peak of the T-wave of the electrocardiogram. A measure of the current required to initiate fibrillation during the vulnerable phase is the Ventricular Fibrillation Threshold (VFT) measurement.

Since the action potential duration may be shortened or lengthened under various abnormal circumstances, refractory periods may be correspondingly altered. For example, hypoxia characteristically decreases the action potential duration, while ischemia lengthens its duration. Conditions that primarily alter the action potential plateau would probably result in changes to the absolute refractory period as opposed to the relative refractory period. It is the changes in both the action potential and refractoriness that are thought to be the precursors of cardiac arrhythmias.

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ELECTROPHYSIOLOGY OF SUDDEN CARDIAC DEATH

Sudden cardiac death results from the development of cardiac arrhythmias, particularly ventricular fibrillation or ventricular standstill. These cardiac arrhythmias are caused by abnormalities in either electrical impulse formation or propagation. The abnormalities in impulse formation are likely to be the result of increased normal automaticity or the occurrence of abnormal automaticity while changes in the propagation patterns, such as the development of re-entry, may be due to cell membrane properties or changes in cell-to-cell coupling. 18

The mechanism of cardiac fibrillation that is thought to represent that found in hypothermia is the circus (re-entrant) theory of Garrey¹⁹ and Lewis²⁰. The re-entry theory postulates repetitive re-excitation of cardiac tissue by a cardiac impulse re-entering an original area of excitation. As stated by Lewis, three factors are important to the development of re-entrant excitation: (1) the length of the conducting pathway, (2) the conduction velocity, and (3) the duration of the refractory period. A relatively long conduction pathway, a slow conduction velocity, and a short refractory period would tend to favor the development of re-entrant excitation leading to fibrillation. Any one or a combination of these events would allow re-entry of the cardiac impulse into the original area of excitation after it is no longer refractory.

Re-entry has been considered to occur in both a macro and a micro sense. An example of macro re-entry would be that which occurs in so called "circus movement" tachycardias, where one wavefront circulates

about the cardiac structures. Micro re-entry implies the ability of re-entry to occur in a small cluster of cells and depends upon the presence of very slow conduction²¹. When micro re-entry does occur, it is very difficult, if not impossible, to differentiate it from enhanced automaticity since it may be impossible to identify the various limbs of the re-entry circuit, as is possible when macro re-entry is present. Re-entry of any type depends upon a critical balance of conduction and refractoriness and always requires the presence of unidirectional block²².

Acute myocardial ischemia (diminished flow of oxygenated blood to a portion of the myocardium) is often used as an intervention in promoting the development of ventricular arrhythmias, including fibrillation. Aside from ischemia resulting from the development of atherosclerotic coronary artery disease, ischemia can be the result of an acute coronary spasm or other sudden obstructions to coronary artery flow. The fact that ischemia could be relatively long lasting, depending upon the mismatch between coronary blood flow and the requirements for such flow, might lead to the development of infarction. The obstruction might be transient, and during reperfusion, there might be other special conditions unique to reperfused tissue²³. The ischemia can cause a number of biochemical and electrophysiological abnormalities, each of which could and probably does increase the ventricle's vulnerability to ventricular fibrillation.

In a single fiber, the induction of acute ischemia results in a decrease in resting potential, a decrease in maximum rate of rise and overshoot of the action potential upstroke, and a decrease in the action

potential duration, which is followed by an increase in the duration of the action potential ²⁴. When time dependent refractoriness occurs, there are changes in automaticity and in excitability. However a great problem in the use of single fiber models in ischemia is that the fibers are superfused in a bath, which results in the prevention of accumulating metabolic end products.

Acute ischemia induces changes in the intact heart which can largely be described from the single fiber model. These changes include very slow impulse propagation and fractionation of activation wave front, particularly at the epicardium, and an increase in the dispersion of conduction and refractoriness ²⁵. It has been shown that the inhomogeneities of metabolic and electrical changes are more marked at the lateral margins of the ischemic region, but they also occur at the center of the zone ²⁶. These inhomogeneities result in voltage differences between adjacent cells which result in a current flow, particularly at the lateral margins of the ischemic zone. The various abnormalities result in a decrease in ventricular fibrillation threshold. It has also been shown that reperfusion results in a series of marked electrophysiologic changes which can lead to the development of ventricular fibrillation ²⁷.

Covino and D'Amato in 1962 showed that in the presence of hypothermia, conduction velocity was slowed and refractory period increased to the same degree as the temperature of experimental dogs was decreased from 37 to 25 degrees Celsius, but beyond 20 C, the prolongation of conduction time (slowing of velocity) was greater than the increase in refractory period. The ratio of conduction velocity to refractory period

was then shown to correlate with an increased tendency toward ventricular fibrillation as measured by ventricular fibrillation threshold (VFT) 28.

In recent years it has been proposed that a spatial inhomogeneity or dispersion of refractoriness is the cause of myocardial re-entry^{29, 30,31,32}. The dispersion of refractoriness creates "islands" which disrupt and fractionate the spreading wave of ventricular depolarization. The wavefront fractionation makes it possible for small waves of depolarization to re-enter the temporarily refractory regions, possibly resulting in macroscopically observable rhythm disruption. This hypothesis suggests a relationship between the degree of dispersion throughout the myocardium and the relative susceptibility to dysrhythmias. To bring the two other theories of dysrhythmogenesis into the picture, ectopic activity can be thought to create a spatial dispersion of refractoriness in that an ectopic focus only acts upon a small portion of the myocardium. Hypothermia has been shown to increase the spatial dispersion of refractoriness as well as slowing conduction velocities and increasing refractory periods. Coronary artery disease can cause a spatial dispersion of refractoriness as a result of metabolically induced changes in the regions of ischemia. Conduction velocity will also be slowed in ischemic tissue. The concept of dispersion of refractoriness serves to provide a unifying and simplifying hypothesis with which to view the advent of re-entrant ventricular dysrhythmias.

Finally, it is important to keep in mind that sudden cardiac death can occur in settings other than ischemia and that many questions regarding the electrophysiologic changes induced by special situations

require answers. These settings include the long QT syndrome, both congenital and acquired, the Wolff Parkinson White syndrome³³, sudden cardiac death occurring in the presence of aortic stenosis or mitral valve prolapse, and the sudden infant death syndrome.

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EXPERIMENTAL PROCEDURE

The first group of experiments were performed on twenty mongrel dogs, 20 - 30 kg. weight, anesthetized with sodium pentobarbital (30 mg/kg intravenously). Lead I surface ECG was used for continuous monitoring and for recording signals for off-line analysis. Lead I was chosen because in this lead the ratio of the amplitude of the pacing stimulus artifact to the amplitude of the QRS complex was usually the smallest. The lead I recording was occasionally modified to minimize the pacing artifact by minor shifting of the electrode location. Electrode location, once optimized, was not changed during the course of an experiment. Aortic blood pressure (ABP) and central venous pressure (CVP) were monitored and recorded throughout the experiments. Monitoring was done using an Electronics for Medicine VR-16 SIMULTRACE recorder, with the ECG amplifiers set for 0.04 Hz to 500 Hz bandpass filtering. All the physiologic measurements were continuously recorded on a Hewlett-Packard 3968 instrumentation recorder in its FM mode, with dc to 625 Hz bandpass. Respiration was accomplished mechanically with a Harvard Apparatus ventilator. Normal temperature was controlled with the aid of a heating pad and an infra red heat lamp. All studies were performed during atrial pacing. Hypothermia, tachycardia, and acute myocardial ischemia were applied to reduce the VFT.

The hypothermia experiments were carried out in closed chest preparations. Transvenous bipolar electrodes were advanced to the right atrium for pacing, and to the right ventricle for VFT measurement. The placement of the intraventricular catheters was repeatedly checked by measuring the electrograms through their electrodes. After

heparinization, blood from the carotid artery was passed through a water cooled heat exchanger and returned through the jugular vein. Upon cooling, the animals were maintained at a rectal temperature of 28-30 degrees Celsius.

To perform the myocardial ischemia experiments, the heart was exposed by mid-thoracotomy, and the left anterior descending (LAD) coronary artery, at the level of the third diagonal, was prepared for occlusion by passing a ligature around the artery. In these experiments, the SA node was crushed and the right atrium was paced by bipolar epicardial electrodes. Two sets of ventricular electrodes were attached to the left ventricle for epicardial electrogram recording (with the same equipment and amplifier settings used for surface ECG measurements) and for subsequent VFT determination. Each set included a pair of screw type electrodes (Medtronics #6917-35AT) which were placed 2 cm apart. Both sets were placed on the free wall of the left ventricle, proximal to the second diagonal and out of the range of the ischemic zone. The 10 minute transient ligation was repeated three to five times, while the first ligation was always ignored because of its anomalous response compared to all subsequent ligations³⁴.

The tachycardia experiments were performed on closed or open chest preparations while the animals were maintained at a rectal temperature of 37-38 degrees Celsius. Atrial pacing was accomplished either via transvenous right atrial bipolar electrodes, or bipolar epicardial electrodes.

A second series of hypothermia experiments was performed on a group of sixteen mongrel dogs. Anesthesia was accomplished with a solution of Urethane-Chloralose (400 mg/kg Urethane, 40 mg/kg Alpha-Chloralose in saline solution). A canine Frank surface lead arrangement was used to generate three orthogonal vectorcardiograph leads, which were recorded as individual channels for later use in generating the SCG. Hypothermia was induced as detailed above.

Ventricular fibrillation thresholds were determined by the gated pulse train technique, according to the methods of Han³⁵. The pulse train was initiated 60 msec following the R wave, and was terminated 200 msec later. The pulses were 2 msec in width and were delivered at a rate of 100/sec. The pulse train was activated every 30 seconds and the current amplitude increased at each trial until fibrillation was accomplished. Following each VFT determination, the animal was defibrillated within 10 seconds, using 25 Joules with epicardial paddles in the open chest animals, and 250 Joules with external paddles in the closed chest animals. A recovery period of 15 minutes was allowed after each VFT determination. Generally, VFT measurements were then repeated at least once again under identical conditions, and when a discrepancy of more than 5% occurred, an additional measurement was made or the data was not included in the analysis.

The experimental procedure was initiated with a set of control measurements carried out at several pacing frequencies. At each state physiological data was recorded over a period of at least 10 minutes to obtain stable data of sufficient duration for the analysis. Then the VFT

was determined for each state. Following the control sequences, either hypothermia or LAD coronary artery ligation was chosen as the intervention. During the hypothermia studies, a decrease in temperature was attained and a sequence of measurements made at different atrial pacing rates. At each heart rate a 10 minute recording of physiologic data was followed by a VFT determination. In the LAD artery ligation studies, the LAD artery was ligated multiple times for 10 minute periods, separated by a 20 minute recovery. At each heart rate, the physiologic data were recorded during the period two to eight minutes following the ligation. The VFT was determined at subsequent ligations during the same period of two to eight minutes following the initiation of the occlusion.

For the hypothermia and coronary artery ligation experiments, each part of control and post-intervention electrogram recordings and VFT's were always obtained at identical pacing rates. The atrial pacing rate used was 200 beats per minute, or if this was not possible we used the highest atrial pacing rate which resulted in a one-to-one atrioventricular conduction in both control and post-intervention states. The tachycardia experiments were conducted with baseline recordings at 140 beats per minute, while the intervention pacing rate was 200 beats per minute. In the ligation and tachycardia interventions surface and/or epicardial electrograms were recorded. In the hypothermia experiments only surface electrograms were recorded. In the ligation and tachycardia experiments, the reported epicardial TWAI's (T Wave Alternans Index) represents root mean square averages of the TWAI's obtained from analysis of the simultaneously recorded epicardial electrograms. Within each analysis group (hypothermia- surface, ligation- surface, ligation- epicardial,

tachycardia- surface, tachycardia- epicardial), each experiment corresponds to a different animal.

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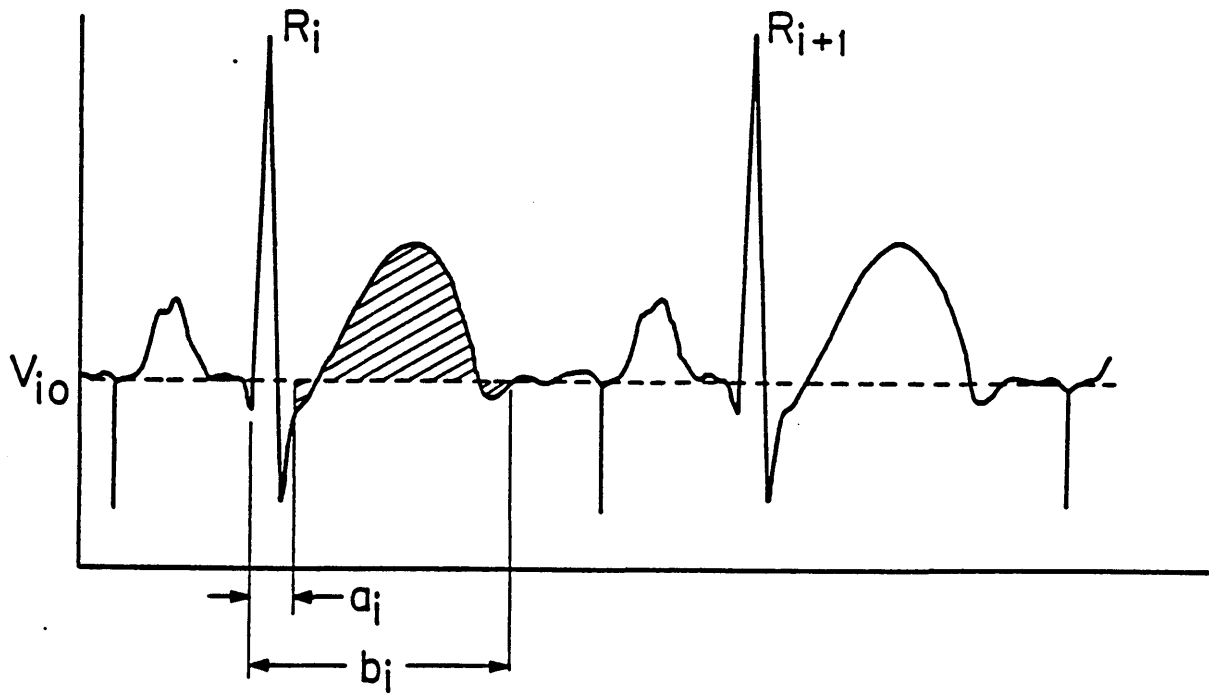
DATA ANALYSIS

The analog signals (respiratory activity, arterial and central venous blood pressures, surface and/or epicardial ECG) recorded on magnetic tape during the animal experiments were analyzed off-line.

The output from the Hewlett-Packard 3968a instrumentation recorder was connected, through gain ($\times 10$) and filtering (0.125 Hz to 68 Hz bandpass) amplifiers, to a dedicated 8085 microprocessor system. The ECG channel was sampled at a rate of 360 Hz and processed by an algorithm based on feature extraction and clustering to detect and classify QRS complexes³⁶. After detection, a cardiac block was set up for each beat. Each block contained the QRS classification, the RR interval, the absolute time of the R-wave occurrence, the peak T-wave value, and the energy of the T-wave (the integral over the duration of the T-wave of the square of the ECG voltage minus its baseline). Simultaneously, the other physiologic signals (CVP and arterial blood pressure) were filtered through a 2 Hz two pole analog filter to reduce aliasing, then sampled at 4Hz. The sampled values were temporarily stored in an eight second long circular buffer. Each ECG parameter block was stored in a data file on a floppy disk following a sample block containing the the samples of the other physiological signals after the previous and before the current QRS block. The resultant data file, at least 1024 cardiac blocks long, was then analyzed using a similar 8085 microprocessor system.

After QRS detection, time delimiters were imposed. When an isoelec-

tric ST segment was present, the first delimiter was set at the first deflection of the T-wave. The second delimiter was set just following the end of the T-wave. There was an exception to this rule when the pacing rate was high and the P wave merged with the previous T-wave (which happened occasionally during hypothermia). Under such conditions the second delimiter was placed just before the stimulation artifact. Thus the P-wave was always excluded from the analysis. The energy of the T-wave (the square of the ECG voltage minus the baseline, integrated over the time interval) was calculated; see Figure 2. Because the quantity of interest was the fluctuations of these values around their mean, the results were not sensitive to the exact choice of the two delimiters.



$$E = \int_{t=a_i}^{t=b_i} (V_T(t) - V_{i0})^2 dt$$

Figure 2.
Crosshatched area defines the T wave energy with respect to baseline voltage V_i

The T-wave energy was computed for 1024 successive beats. A 1024 point time series was constructed; the i th point in the time series equaled $(E_i - E)/E$, where E_i is the value of the T-wave energy of the i th beat, and E is the arithmetic average of all 1024 measurements of the T-wave energy. The time series for the T-wave energy was then analyzed by computing the histogram, serial autocorrelation coefficients and power spectrum (using a Fast Fourier Transform technique). The "T-wave Alternans Index" (TWAI) was computed from the power spectrum of the T-wave time series, by measuring the square root of the height of the last point of the spectrum above the noise level, defined as the average of the preceding ten points of the spectrum. The last point on the spectrum corresponds to the energy of the T-wave fluctuations at one half the pacing frequency because one number, the T-wave energy, is generated for each heartbeat, and the highest frequency obtained by the Fourier Transform is exactly one-half the "sampling" frequency of the data.

The distributions of TWAI measurements obtained were found to be highly non-Gaussian. Therefore, all tests of significance were computed using nonparametric statistical methods. In each set of experiments, the significance of intervention induced changes in TWAI and VFT were tested using the paired Wilcoxon signed rank test³⁷. The correlation between changes in TWAI and changes in VFT were analyzed using the sign test and calculation of correlation coefficients.

ANALYSIS OF THREE DIMENSIONAL VECTORCARDIOGRAM EXPERIMENTS

The three orthogonal surface leads were recorded onto individual channels of the Hewlett Packard 3968A FM tape recorder. The recordings

were played back through an analog post-processor which squared the three input voltages, summed the results, and took the square root of the sum:³⁸

$$V = A * \sqrt{(X^2 + Y^2 + Z^2)}$$

where

- V= the Scalar Cardiogram voltage
- A= arbitrary gain
- X= ECG channel 1
- Y= ECG channel 2
- Z= ECG channel 3

As the mean value of the calculated measures was not of significance, the gain A was adjusted so as to obtain the maximum dynamic range. The Scalar Cardiogram (SCG) Voltage, V, was analyzed as was detailed above for the ECG voltage, with the exception that in this case the integrated area under the SCG can be defined as the T wave energy.

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RESULTS OF EXPERIMENTATION

A typical section of an ECG recording is shown in Figure 3 for both the control and intervention states. Primary analysis of the data resulted in a time series consisting of one value corresponding to the T-wave morphology parameter (in this case, the T wave energy) for each heart beat. A time series is shown in Figure 4. The fluctuations in the T-wave morphology can be visualized by constructing the histogram, auto-correlation function, and the power spectrum of the time series.

The histogram is derived from a time series of 1024 consecutive heart beats. The T-wave energy parameter, X_i , is computed from:

$$X_i = \frac{E_i - \bar{E}}{\bar{E}}$$

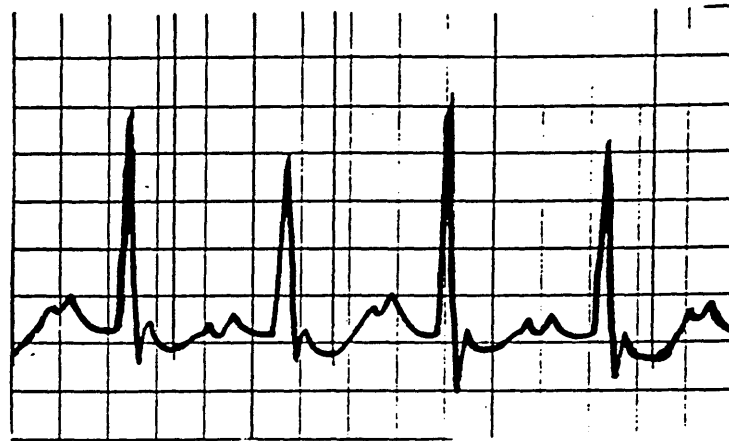
$$\bar{E} = \frac{1}{N} \sum_{i=0}^{N-1} E_i$$

where: $N = 1024$

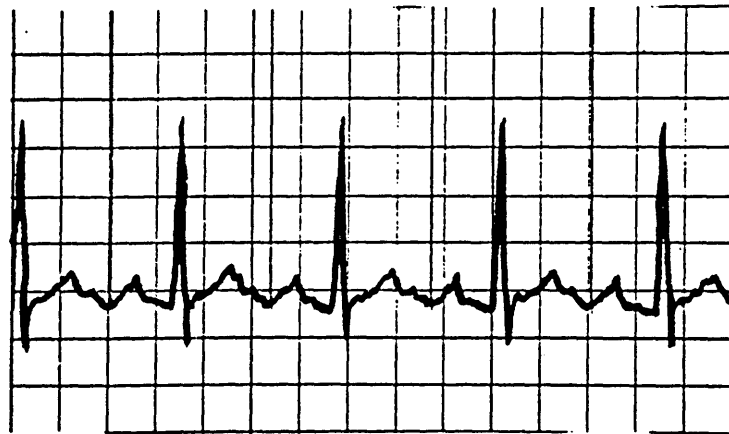
E_i = T wave energy parameter of
ith beat in time series

\bar{E} = Arithmetic mean of E_i s

Figure 5 displays a histogram of the normalized T-wave energy time series both before and after the induction of hypothermia. In the normothermic animal, the histogram presents itself as a narrow peak of nearly Gaussian distribution. Upon lowering the dog's internal temperature, the distribution widens with the appearance of two peaks, indicating the development of two distinct types of T-waves, based upon their associated energies.



T = 30.2°C VFT = 34



T = 37.0°C VFT = 49

Figure 3.
Representative ECG's of normothermic
and hypothermic dogs.

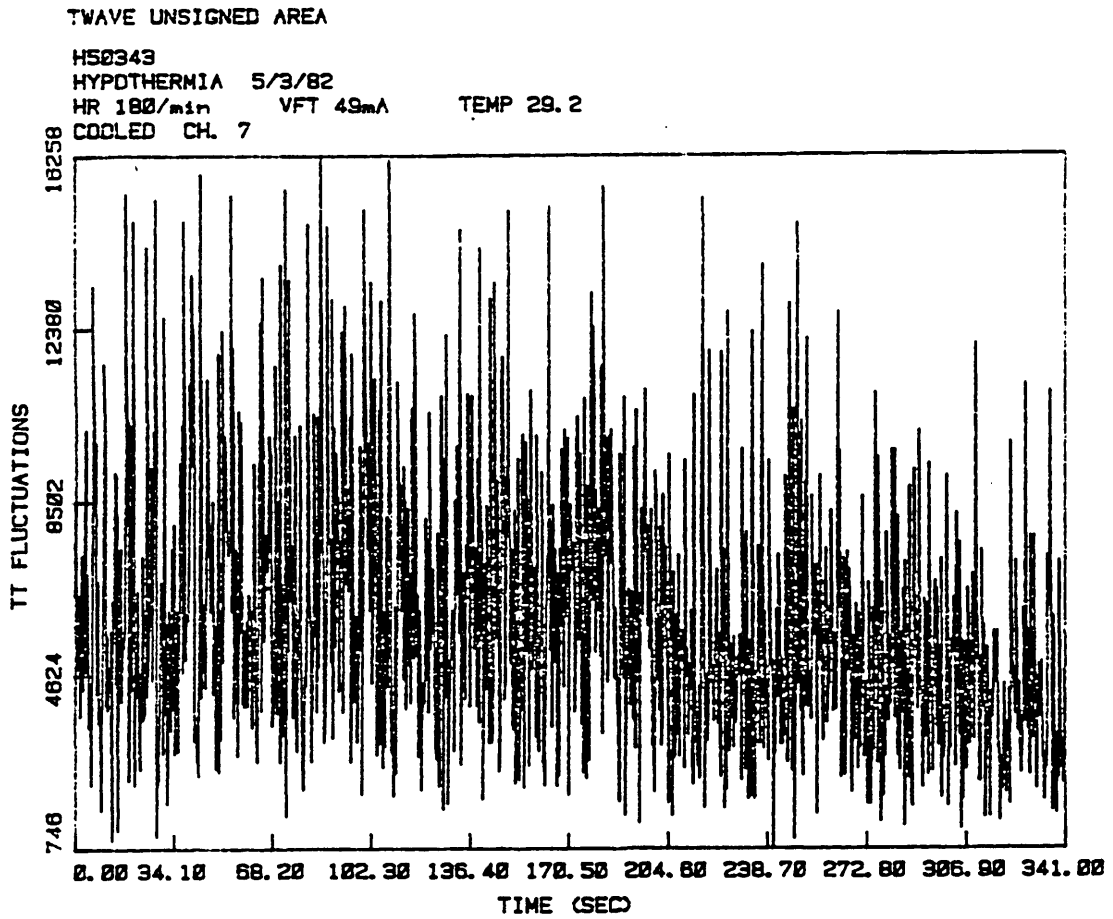


Figure 4.
A time series of T wave energy parameter
computed from 1024 beats.

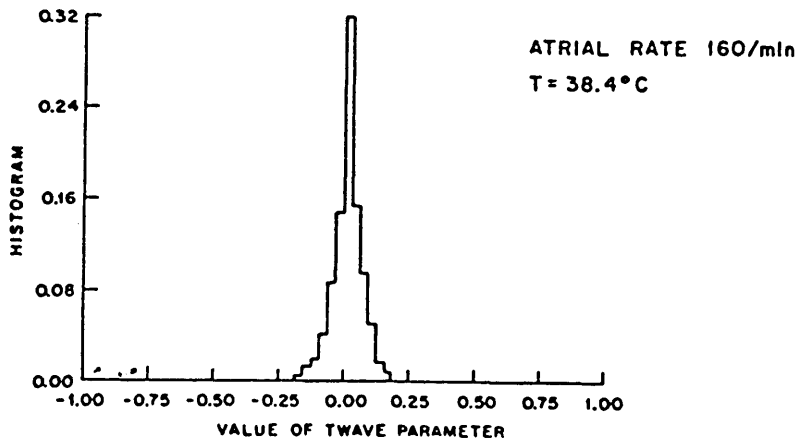
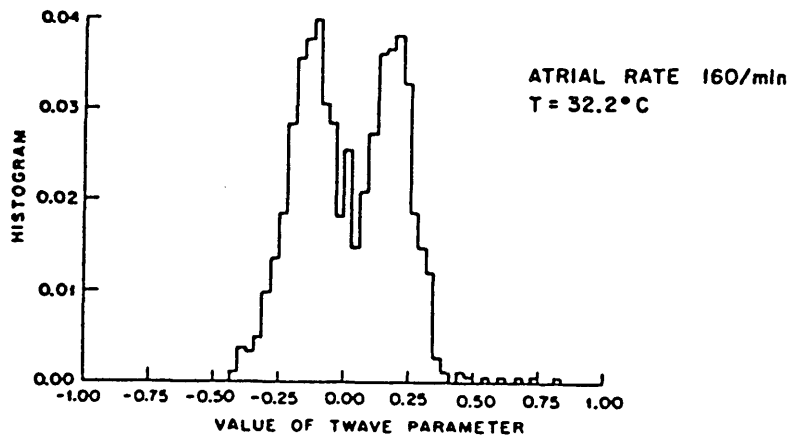


Figure 5.
Histograms of T wave parameter for normothermic and hypothermic dogs. Note the bimodal distribution of the histogram in the hypothermic dog.

While the histograms can help to ascertain the presence of different T-wave subpopulations, it cannot provide information relative to the time dependence between T-waves. To obtain a quantification of temporal fluctuations, the serial autocorrelation coefficients, R_j , of the time series were determined:

$$R_j = \frac{1}{N-j-1} \sum_{k=0}^{N-1} X_{j+k} X_k$$

The serial autocorrelation coefficient is a measure of the degree to which the morphology of one T-wave corresponds with that of a T-wave occurring j beats later. From Figure 6, it is apparent that, at control temperatures, the serial autocorrelation coefficients are of low amplitude, while in the presence of hypothermia the values increase substantially and alternate in sign. This is a mathematical indication of the development of T-wave electrical alternans.

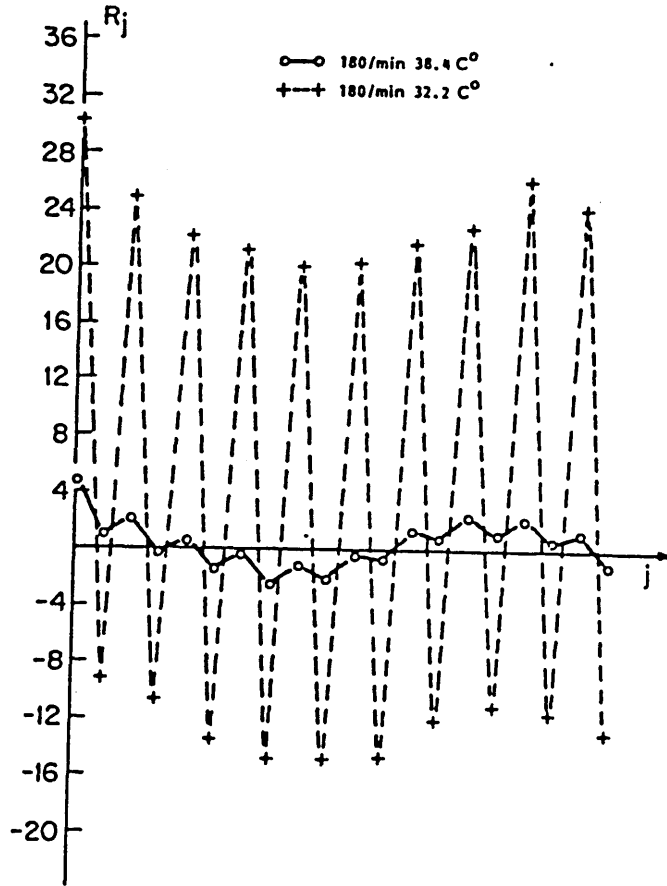


Figure 6,
Auto correlation coefficients for the
normothermic and hypothermic dog.

The serial autocorrelation coefficients are not, however, very useful in quantifying the degree of alternans. Autocorrelation coefficients can be modulated by mechanical motion which results from the animal's breathing. It is therefore advantageous to calculate the power spectrum of the fluctuations in the T-wave morphological parameter, and measure the amplitude at a frequency corresponding to one-half the pacing frequency (this is also the Nyquist frequency, that which is the highest frequency computed). Figures 7 and 8 show the power spectra of the T-wave energy fluctuations in a normothermic and a hypothermic dog, respectively. The hypothermic dog displays a peak at 1/2 the pacing frequency, corresponding to a pattern of T-wave alternans. Fluctuations are also manifest at lower frequencies; these correspond to T-wave fluctuations resulting from respiratory activity and the beat-to-beat fluctuations in autonomic nervous system activity ³⁹. To quantify the T-wave alternans as observed in the power spectrum, the T-wave Alternans Index (TWAI) was defined as the square root of the amplitude, above the mean background noise level (defined as the average of the ten preceding points of the spectrum), of the peak in the power spectrum located at exactly one half the pacing rate; the TWAI is developed graphically in Figure 9.

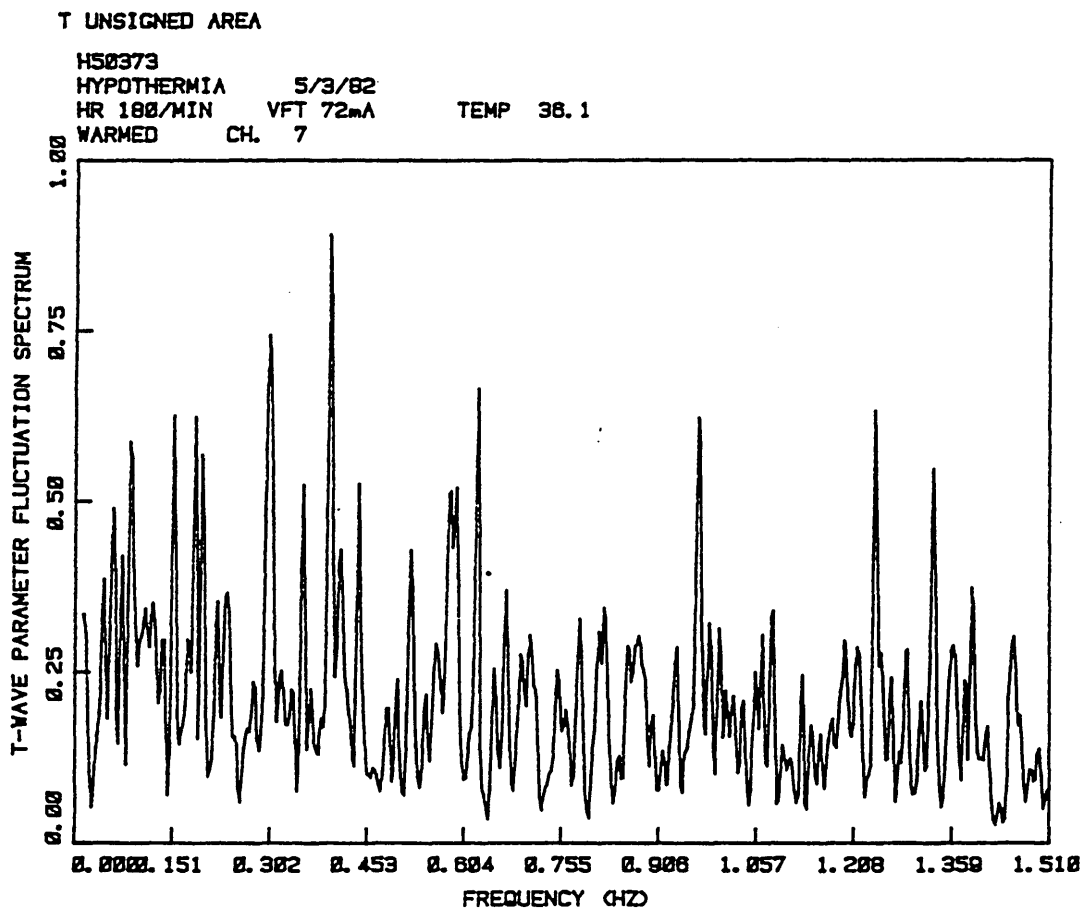


Figure 7.
Power spectrum for dog at normal temperature.

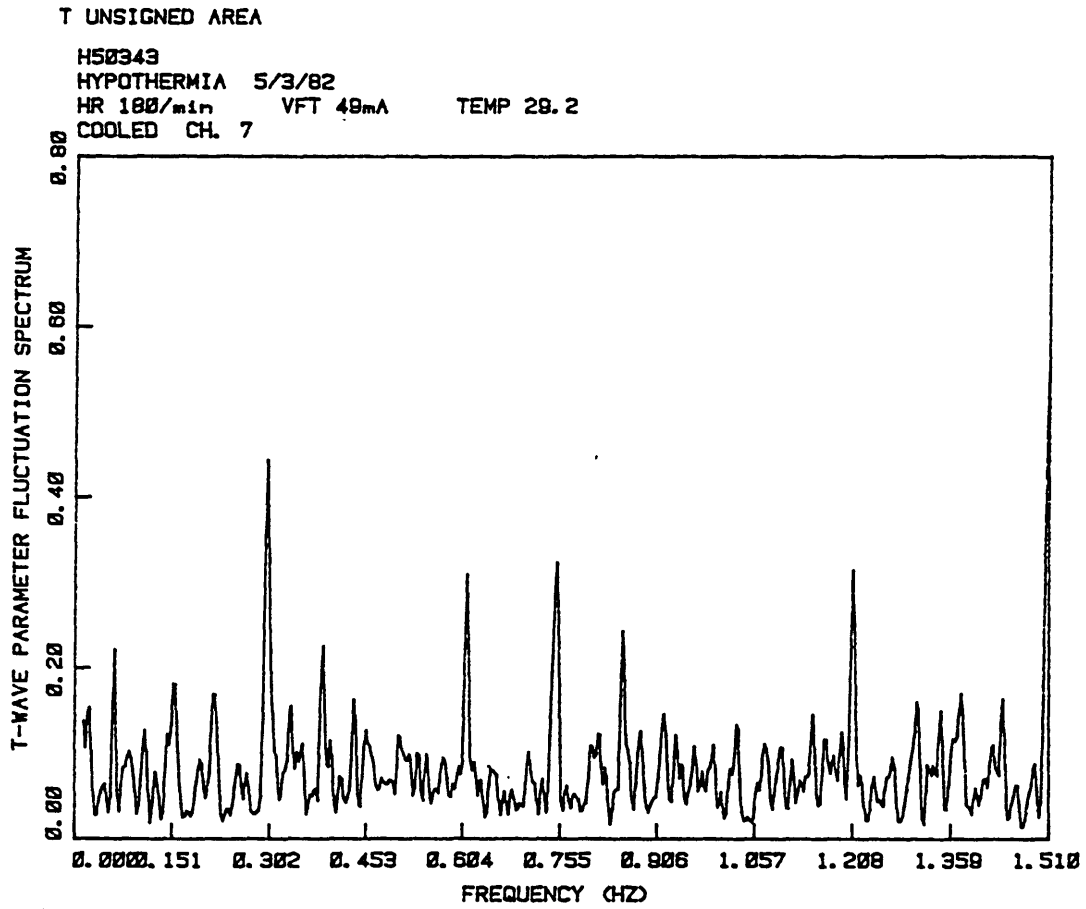


Figure 8.

T wave fluctuations power spectrum for the hypothermic dog. Note the peak at 1.51 Hz, which corresponds to one half the heart rate frequency.

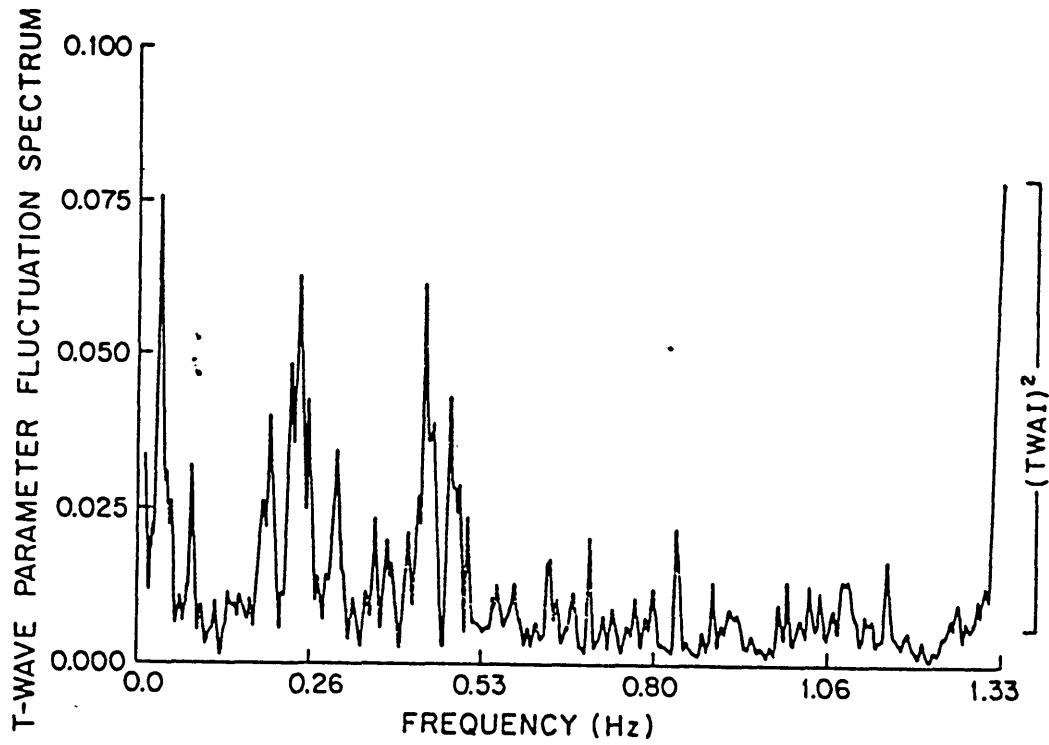


Figure 9.
A T wave fluctuations power spectrum,
graphically depicting the computation
of the T Wave Alternans Index (TWAI).

Previous experiments ^{40, 41, 42} had demonstrated that the degree of T-wave alternans increased as VFT was reduced. The T-wave alternans was not always discernible by eye, but was easily quantified through the TWAI measurement. This report presents the findings noted above, with the addition of further tests to determine the correlation between changes in the TWAI and VFT under three different interventions that have been shown to cause decreases in VFT ^{43, 44, 45} : hypothermia, coronary artery ligation, and tachycardia.

In the compilation of seven hypothermia experiments, a mean reduction in VFT was induced by cooling the animal's core temperature from 37 to 30 degrees Celsius. A corresponding increase in TWAI was observed in six of the experiments. The mean TWAI increase from .26 to 1.85 ($p < .03$). Figure 10 presents a graphical representation of the data.

A separate series of sixteen hypothermia experiments was done to determine whether the observed changes in TWAI were due to mechanical or electrical angular changes of the repolarization wavefront propagation, or due to alternans in the electrical conduction process. The Scalar Electrocardiogram (SCG) was computed as a directionally insensitive measure of cardiac electrical activity. Figure 11 displays three orthogonal ECG leads together with the corresponding SCG. We found that TWAI of the SCG increased in 17 of 19 trials conducted at various pacing rates, while the VFT was reduced by hypothermia in 17 of the trials. The results from this series of experiments are compiled in Figure 12.

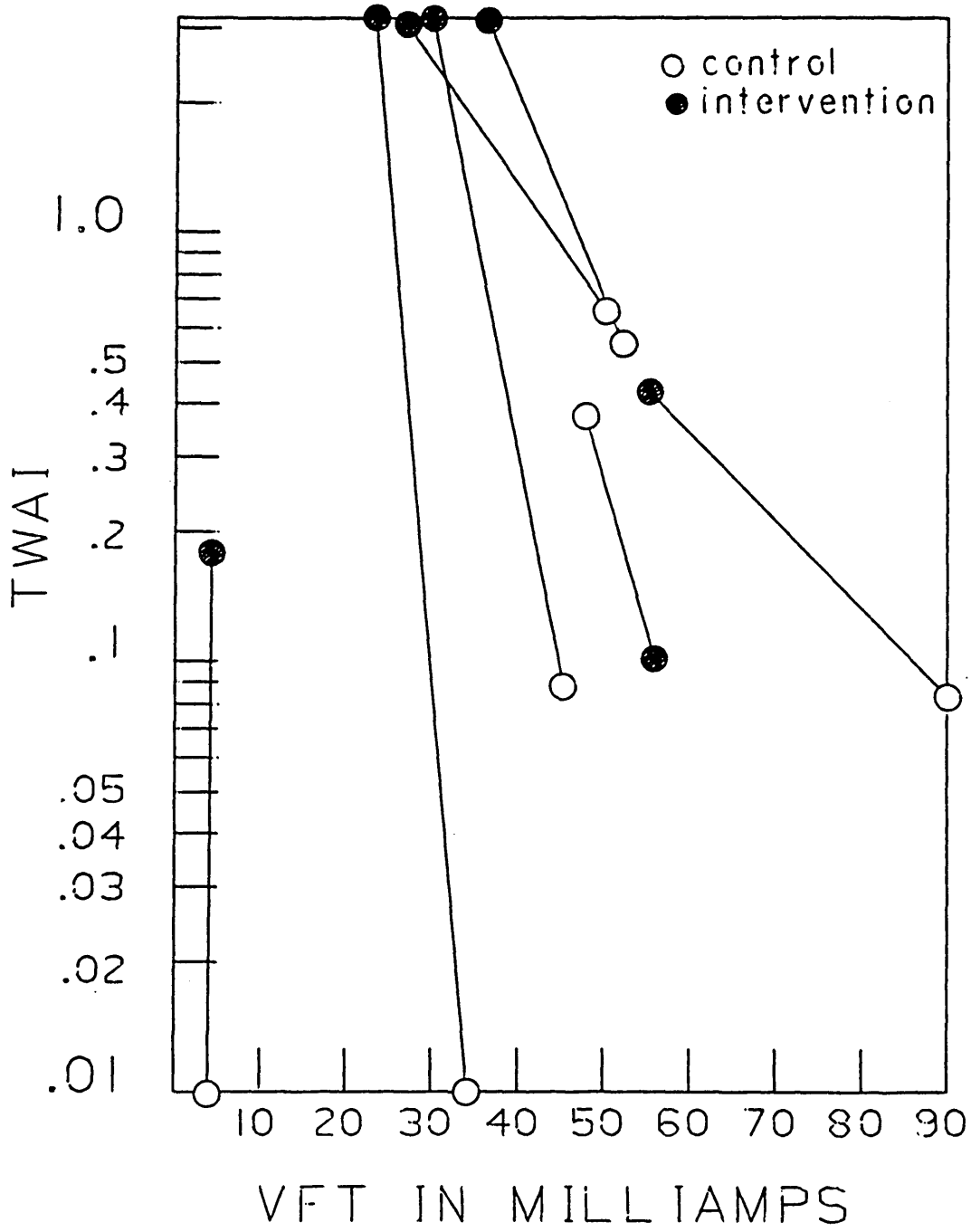


Figure 10.
Summary of hypothermia experiments
Surface ECG

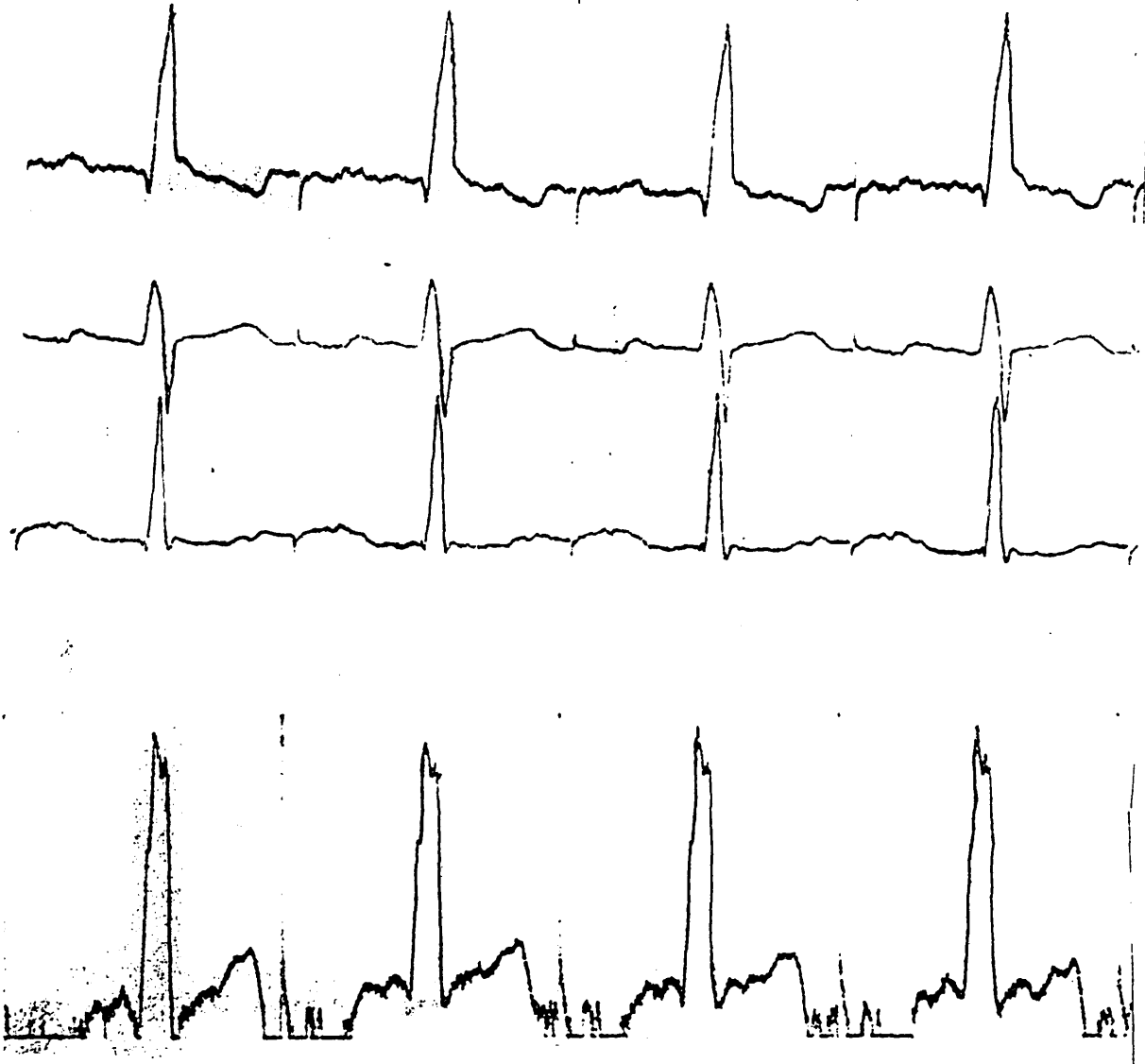


Figure 11.
Electrogram of three orthogonal
ECG leads and the corresponding
Scalar Cardiogram (SCG) (lowest
trace). Dog is paced at 120 bpm

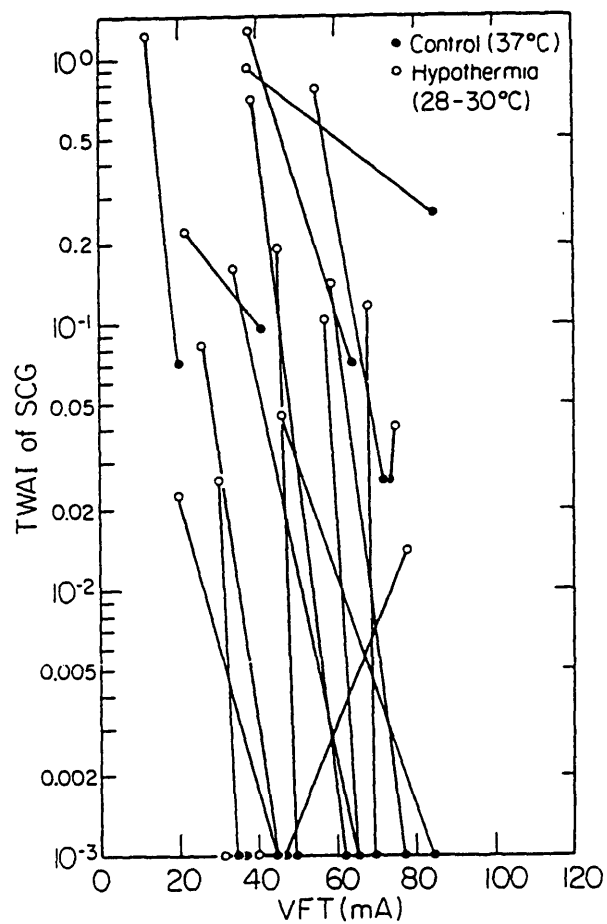


Figure 12.
Summary of hypothermia experiments
using the Scalar Cardiogram (SCG).

A reduction in VFT was observed in all experiments in which the left anterior coronary artery was occluded. Epicardial recordings yielded a mean increase in TWAI from .06 to .33 ($p < .001$) as a result of ligation, while the VFT showed a mean decrease of 13 mA ($p < .001$). Figure 13 summarizes the results of the 11 ligation experiments from which epicardial electrograms were recorded. The surface electrocardiogram showed similar findings in the ligation experiments. Seven out of ten experiments demonstrated a rise in TWAI computed from surface recordings. The mean TWAI rose from .06 to .2 ($p < .08$) as a result of the intervention, while the VFT fell an average of 12.5 mA ($p < .001$) during ligation and subsequent release. Figure 14 details the findings for ligation experiments and surface ECG recordings.

An increase in the heart rate from 140 to 200 beats per minute resulted in a mean decrease in VFT of 12 mA ($p < .08$), and an absolute decrease in VFT in 5 of 6 experiments. Tachycardia resulted in a rise in TWAI from epicardial electrograms in all six experiments (mean rise in TWAI was from .02 to .15, $p < .02$). Surface electrocardiogram recordings yielded an increase in TWAI in seven of ten experiments (mean rise .09 to .37, $p < .09$), while the VFT decreased as a result of tachycardia in all ten cases (mean difference 15 mA, $p < .001$). Figures 15 and 16 display the results of the tachycardia experiments.

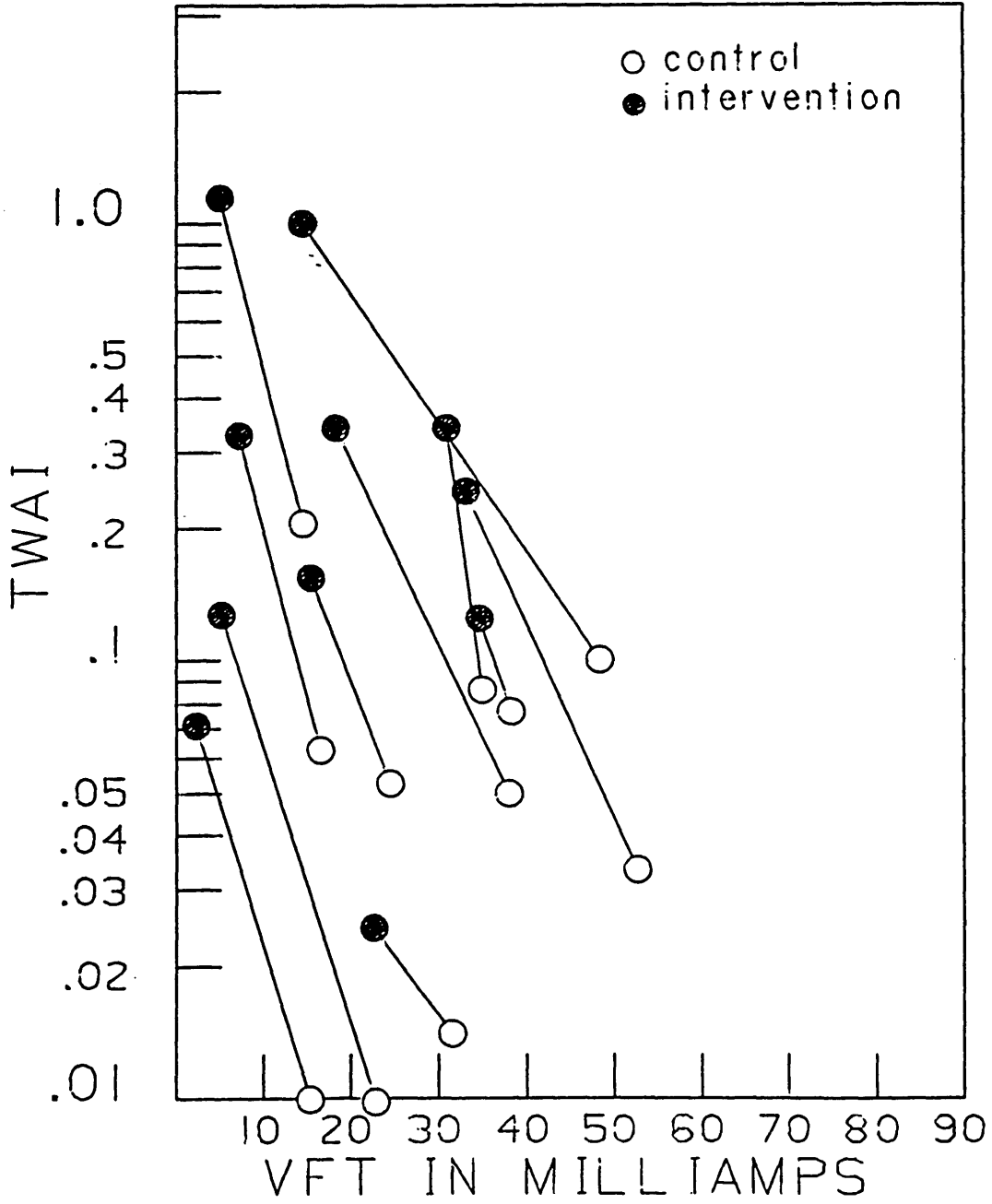


Figure 13
Ligation Experiments
Epicardial ECG

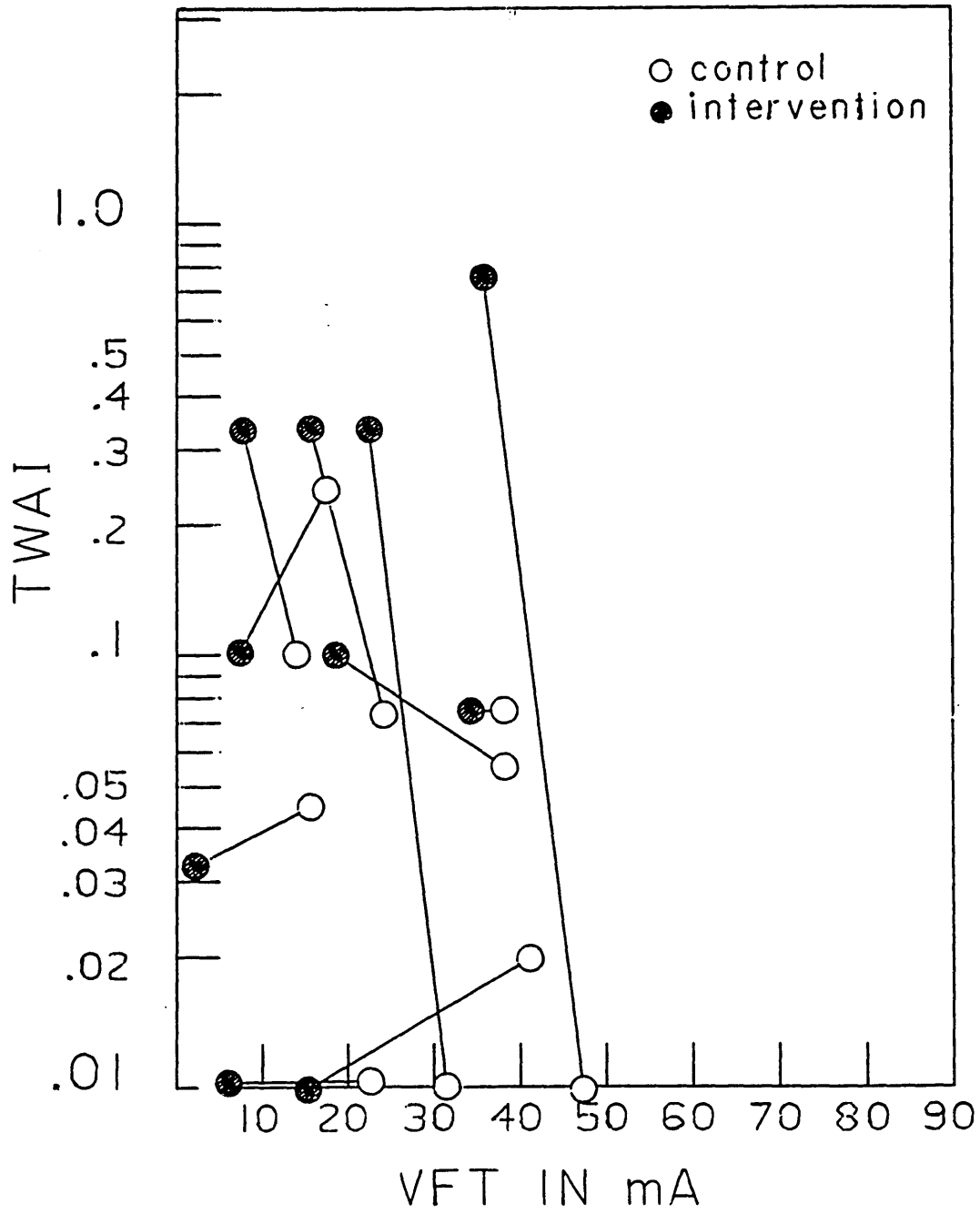


Figure 14 .
Ligation Experiments
Surface ECG

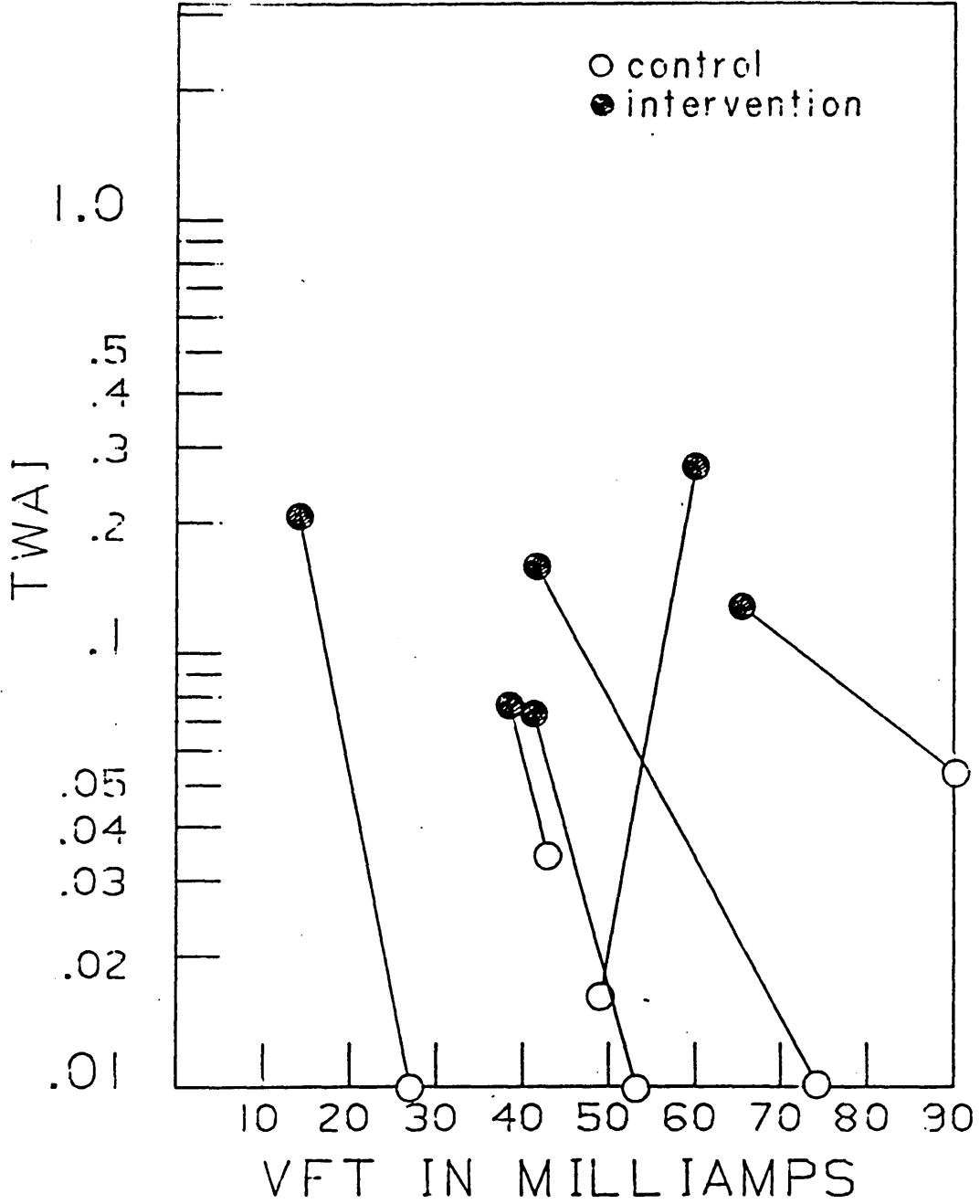


Figure 15 .
Summary of tachycardia experiments.
Epicardial ECG

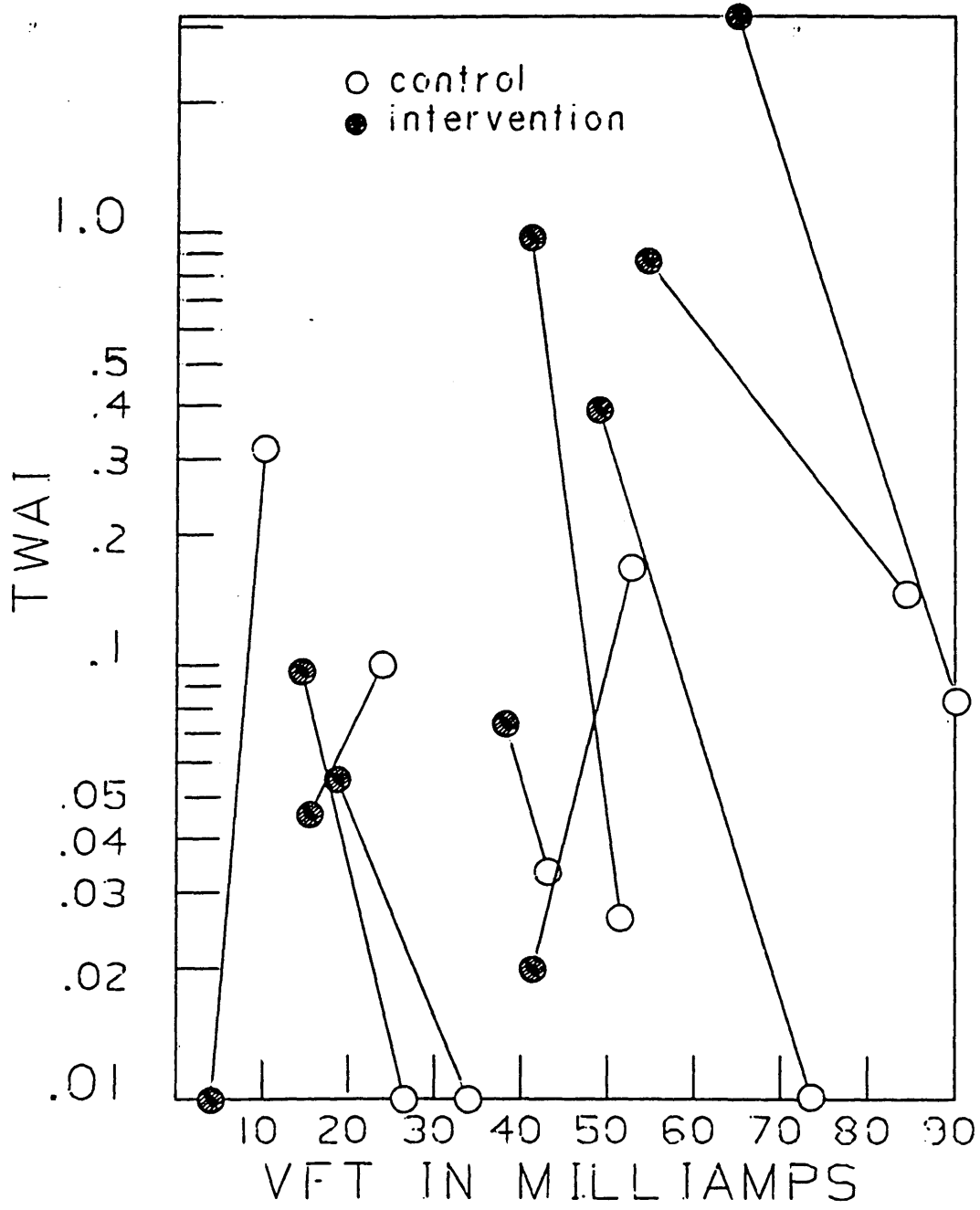


Figure 16 .
Tachycardia experiments
Surface ECG

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DISCUSSION

We have shown that there exists a statistically significant correlation between fluctuations in the morphology of the electrocardiogram and ventricular vulnerability to fibrillation. Specifically, as ventricular fibrillation threshold was reduced by means of hypothermia, coronary artery ligation, and tachycardia, alternans in the T-wave complex developed, and the degree of such alternans could be quantified by the T-wave Alternans Index (TWAI). The alternans also developed in an angle-independent measure of cardiac activity, the Scalar Electrocardiogram. This second observation suggests that the observed alternans is related to the spatial and temporal patterns of cardiac repolarization, and not simple mechanical or electrical rotations of the myocardium about its axes.

The findings of electrical alternans in the electrocardiogram are not new. Hering first reported the development of alternans in an experimental canine preparation in 1908⁴⁶. Lewis, in 1910, reported the first clinical evidence of electrical alternans in humans. He observed the development of alternans under conditions of tachycardia and myocardial degeneration⁴⁷. In 1913, George Mines proposed that the alternans he observed in frog and turtle heart preparations was due to lowered excitability of a portion of segment of the heart muscle⁴⁸ [49].

The feeling that electrical (and mechanical) alternans was the result of a locus of decreased myocardial activity was postulated throughout the first half of the century. Brody and Rossman suggested

that alternans was the observed result of two alternating foci of impulse initiation or of two alternating paths of conduction ⁵⁰. Louis Katz wrote in his textbook Clinical Electrocardiography that "the factor underlying all forms of cardiac alternation is a marked prolongation of the refractory phase of the heart." ⁵¹

Coronary artery occlusion was linked to the development of electrical alternans in the laboratory by Hellerstein and Liebow in 1950 ⁵². They found T-wave alternans present in 8 of 9 dogs that survived a coronary artery occlusion (2 dogs died, including one from spontaneous ventricular fibrillation). An explanation of the reason for alternans was as follows : " Following a previous activation an impulse finds some regions of the myocardium still refractory. Consequently, the response in every alternate beat will be abnormal- mechanically or electrically." ⁵³ They also went on to say that one can not differentiate between local areas and the entire myocardium as sources of alternans.

The first report finding electrical alternans in a single fiber preparation was published by Hoffman and Suckling in 1954 ⁵⁴. Kleinfield found that in a frog heart preparation, four distinct types of alternation could be distinguished in a single fiber: 1) the rate of membrane depolarization; 2) the rate of membrane repolarization, 3) the magnitude of the action potential and 4) the magnitude of hyperpolarization ⁵⁵. Thus a means was shown whereby the entire myocardium could participate in alternating activity, rather than specific localized areas as the root of electrical alternation. They noted, however, that not all fibers actively participate in alternation all of the time.

An alternate view on the causes of alternans in the

electrocardiogram was put forth by McGregor and Baskind in 1955. They postulated that the surface electrocardiogram displayed alternans due to the mechanical movement of the heart within the pericardial sac⁵⁶. Mines had noted a similar finding in 1913, correlating alternating mechanical action of the heart with electrical alternans. Although these findings did not correlate to the theories that electrical alternans is due to changes in myocardial refractoriness, they served to demonstrate that similar clinical findings can be explained satisfactorily from different experimental results.

In recent years there have been numerous clinical documentations of episodes involving T-wave alternans. Most of these can be associated with the course of two pathologies: the long QT syndrome and Prinzmetal's angina. In the long QT syndrome, both the Romano-Ward (characterized by a long QT interval and syncopal episodes due to ventricular fibrillation) and Jervell-Lange-Nielson (typified by the additional symptom of congenital deafness) types, electrical alternation in the T-wave often manifests itself just prior to or following syncopal episodes characterized by ventricular tachycardia or fibrillation⁵⁷. They found that, while a prolongation of the QT interval seems to be a stable situation, the advent of T-wave alternans indicates an electrical instability of the myocardium. Specifically, the T-wave alternans was due to an abrupt increase in sympathetic nervous system activity. The evidence of T-wave alternans can be linked to the theories of spatial dispersion when one considers the non-homogenous, asymmetrical nature of cardiac sympathetic innervation. The same authors did a very comprehensive literature search on the long QT syndrome, and found that T-wave alternans was present, but not always reported, in 13 of 28 case

studies of the long QT syndrome.

Prinzmetal's angina is believed to be the result of an acute coronary artery spasm. Approximately 30% of patients suffering from Prinzmetal's angina have demonstrated a degree of ST segment or T-wave alternans⁵⁸. The findings of T-wave alternans following an episode of coronary vaso-spasm are consistent with the belief that myocardial ischemia can result in increased refractory period and create regions of tissue that are susceptible to localized conduction delays and heart block, markers of electrical instability in the myocardium⁵⁹.

We have shown that there is a long history of both experimental and clinical evidence documenting electrical alternans and linking it to ventricular vulnerability. This report suggests that T-wave alternans is not an episodic occurrence, but rather that the development of T-wave alternans can be quantified and linked to the development of potentially malignant ventricular dysrhythmias. The presence of T-wave alternans can be detected by numerical analysis of a direction-independent electrocardiographic parameters even when it may not be evident in conventional single-lead recordings.

While the observed alternans may be the result of individual cells whose electrical properties are alternating in a beat-to-beat fashion, we believe that alternans is the observable manifestation of a number of cardiac cells which can respond only to alternate stimuli. This phenomenon is related to the "dispersion of refractoriness" hypothesis, put forward by Han, et al. in 1966⁶⁰. They assumed a spatial temporal dispersion of myocardial refractoriness, which led to conduction disruptions and the development of re-entrant beats [61].

As the dispersion of cellular refractory periods increases, alternans can develop. The increased dispersion results in some cells having a refractory period longer than the stimulus interval [62, 63, 64,65]. Such cells will only be able to respond to alternate beats, with the outcome of electrical alternans.

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