Slow and Long-Lasting Modulation of Myocardial Repolarization Produced by Ectopic Activation in Isolated Rabbit Hearts

Evidence for Cardiac “Memory”

Angelika Costard-Jäckle, MD, Bettina Goetsch, Matthias Antz, and Michael R. Franz, MD

Prolonged ventricular pacing induces T wave polarity changes that persist long after cessation of pacing. To examine how ventricular repolarization is modulated by prolonged changes in activation sequence, we studied the effect of ectopic pacing on the distribution of action potential durations (APDs) in nine isolated Langendorff-perfused rabbit hearts. A contact electrode probe was used to map right and left ventricular-epicardial monophasic action potentials during three consecutive changes in stimulus site, that is, 1) during 45 minutes of right atrial pacing, 2) during 120 minutes of right ventricular pacing, and 3) again, during 60 minutes of right atrial pacing. During each of these phases, the effect of activation sequence on repolarization was examined by linear-regression analysis of APD on activation time (AT). Results averaged for all nine hearts showed that during the initial atrial-pacing phase, APD was inversely related to AT (slope \(S = -1.63; r = 0.76\)), indicating that sites with earlier activation repolarized later. With the onset of ventricular pacing, the inverse correlation between AT and APD disappeared (\(S = -0.19; r = 0.31\)). Continuing ventricular pacing, however, produced slow changes in APD that restored the inverse relation (\(S = -0.71; r = 0.68\) at 120 minutes; \(p < 0.0002\) versus 5 minutes). Switching from ventricular to atrial pacing again perturbed the inverse correlation (\(S = 0.28; r = 0.35\)) but at 60 minutes of atrial pacing, a significant inverse correlation was reestablished (\(S = -1.25; r = 0.53; p < 0.01\) versus 5 minutes). An inverse correlation between AT and APD tends to synchronize repolarization time (RT, the sum of AT and APD).

Accordingly, the variance coefficient for RT at all recording sites, a measure of repolarization dispersion, was significantly greater shortly after a change in pacing site (4.7±0.3 at 5 minutes of ventricular pacing versus 2.4±0.3 at 45 minutes of atrial pacing, \(p < 0.0001\)) and decreased progressively as pacing at the new site was maintained (3.4±0.4 at 120 minutes of ventricular pacing, \(p < 0.02\) versus 5 minutes). These data indicate that the sequence of ventricular activation modulates the sequence of ventricular repolarization by a yet unidentified process with very slow onset and offset characteristics. This phenomenon of cardiac “memory” may explain T wave changes following prolonged changes in ventricular activation, as seen in intermittent left bundle branch block, after ventricular tachycardia, and in preexcitation syndromes. Short-term changes in ventricular activation (as used during electrophysiologic studies) may not allow for sufficient adaptation of APD to AT, producing greater and possibly arrhythmogenic dispersion of repolarization. (Circulation 1989;80:1412-1420)

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T wave changes can be classified as either primary or secondary. Primary T wave changes have been defined as the result of uniform or nonuniform changes in action potential duration (APD) in the absence of changes in the sequence of activation. Secondary T wave changes have been defined to reflect changes in the sequence of repolarization that result solely from changes in the sequence of activation, without any abnormalities in the duration and shape of action potentials.1–3 However, Chatterjee et al4 and Rosenbaum et al5
demonstrated that prolonged alteration in the sequence of activation caused by ventricular pacing not only caused secondary T wave changes during the period of pacing but that conspicuous T wave changes persisted for a long time after pacing was terminated and a normal supraventricular activation pattern had resumed. Other, apparently related clinical phenomena are transient T wave alterations after intermittent left bundle branch block,6,7 ventricular tachycardia,8,9 extrasystoles,10 or ventricular preexcitation.11 In each, T wave alterations persist after normalization of ventricular activation and, for the most part, in the absence of known myocardial disease that would allow these T wave changes to be classified as primary.

Rosenbaum et al9 noted that prolonged ventricular pacing modulates ventricular repolarization such that the T wave again becomes concordant to the R wave, as during normal supraventricular activation. They interpreted this intriguing finding by attributing to the myocardium the properties of accumulation or “memory” by which the heart “learns” to adjust its repolarization to an altered activation sequence and by which it retains the adapted state long after the activation sequence is normalized. However, basic electrophysiology has not yet provided direct validation that myocardial tissue is capable of such long-lasting “memory” of the past sequence of activation or repolarization.

The present study was designed to examine whether pacing-induced changes in repolarization are indeed due to an intrinsic myocardial property and can occur without extracardiac influences. In isolated Langendorff-perfused rabbit heart preparations (which lack neurohumoral influences), we mapped the distribution and interrelation of activation time (AT), APD, and repolarization time (RT) during consecutive, long-lasting changes in ventricular activation sequence. Our objectives were 1) to determine whether prolonged changes in activation sequence can produce persistent changes in ventricular repolarization, 2) to determine the time course with which these changes develop and dissipate, and 3) to determine how these changes influence the synchrony of repolarization in the whole ventricle.

**Methods**

**Isolated Rabbit Heart Preparation**

Twenty-one New Zealand White rabbits of either sex, weighing 5.0–6.6 kg, were anticoagulated with 75 units/kg heparin i.v. and stunned by a blow to the occiput. After a median sternotomy, the heart was removed quickly and chilled in ice-cold modified Krebs-Henseleit solution of the following composition (mM): NaCl, 118; KCl, 4.7; CaCl₂, 2.5; MgSO₄, 1.2; KH₂PO₄, 1.2; NaHCO₃, 25; glucose, 5.5; and Na pyruvate, 2.0. Human albumin (0.006 mM) was added to the solution. These small amounts of albumin have been shown to significantly increase the stability of the preparation so that the frequency of ventricular fibrillation is drastically delayed, and the effective refractory period remains stable over 4–5 hours of artificial perfusion.12 The cut aortic stump was cannulated and the heart transferred to a warmed Langendorff apparatus. Nonrecirculating perfusion with warmed (34.9±0.2°C), oxygenated (95% O₂:5% CO₂), modified Krebs-Henseleit solution of the composition previously given (pH 7.40±0.02) was initiated at a constant flow rate of 20 ml/minute using a flow roller–pump system (Micro Pump model 31152). Average heart weight was 8.0±0.6 g. The time from killing of the rabbit to initiation of the perfusion was less than 60 seconds. A small needle was inserted through the left ventricular free wall for drainage of thebesian flow. The perfusion pressure was monitored through a branch of the aortic cannula with a sphygmomanometer and was within a range of 60–100 mm Hg throughout the experiment. Bipolar copper wire electrodes were inserted into the right atrial appendage and into the right ventricular free wall near the apex and connected to a custom-built stimulator. The stimulus output could be switched between the two pacing sites without interruption of the pacing frequency. Bipolar platinum wire electrodes were inserted at the ventricular base, and the recorded electrogram was monitored continuously on a Tektronix 5111A oscilloscope.

**Experimental Protocol**

Immediately after the heart was mounted to the Langendorff apparatus, pacing was started through bipolar platinum pacing wires inserted into the right atrial appendage. Another pacing dipole was inserted in the right ventricular apex to be used later in the experiment. Stimuli of 1-msec duration were delivered with a constant current isolated stimulus unit (World Precision Instruments, New Haven, Connecticut) at twice diastolic threshold strength that initially averaged 0.6±0.2 mA and remained constant within 0.2 mA throughout the experiment. The pacing rate was set at 180 beats/min and kept constant throughout the experiment. After an equilibration period of 30 minutes, monophasic action potentials (MAPs) were recorded from 12–20 different epicardial sites with a bipolar contact electrode similar to that already described.13 This electrode has been shown to reproduce with fidelity the activation time and the time course for repolarization of adjacent cells.14 Recordings were made sequentially from each site, using a detailed map of the epicardial surface, to identify the locations from which each recording was made. On average, two thirds of the recordings were made from the left ventricle and one third was made from the right ventricle, with recordings sites spread out evenly over each ventricle’s surface as judged visually. When the center electrode was pressed slightly against the surface of the heart, monophasic action potentials developed and stabilized within 2–6 beats, allowing us to complete MAP mapping at up to 20
sites within 5 minutes. MAP recordings were amplified with a high-impedance, direct-current coupled, differential preamplifier (model 1001, EP Technologies, Mountain View, California) that had a bandwidth of 0 to 5000 Hz. The preamplified MAP and the ventricular electrogram were recorded on a two-channel Gould 2200 S chart recorder at a paper speed of 200 mm/sec.

After mapping studies had been performed at 30 and 45 minutes of atrial pacing, pacing was switched to ventricular pacing and MAPs were recorded from the same epicardial sites as during atrial pacing at 5, 30, 60, 90, and 120 minutes after the onset of ventricular pacing. By simply switching the oscillator from one (the atrial) stimulus output channel to another (the ventricular) output channel, the pacing rate of 180 beats/min was maintained at exactly the same value during the transition from atrial to ventricular pacing. After 120 minutes of ventricular pacing, the stimulus output was switched back to the atrial-pacing wires (again under maintenance of the same pacing rate), and MAP recordings were repeated 5, 30, and 60 minutes after resumption of atrial pacing. During each subsequent mapping study within one experiment, the drawn epicardial surface map was used to reproduce the recording sites of the initial mapping study.

Control Studies

In four experiments, hearts were paced continuously from the right atrium alone, for 4 hours, and epicardial MAP maps were obtained at the same intervals as previously described. The purpose of these control studies was twofold: first, to test the reproducibility of the individual recording sites by repeated measurements from the same sites using the ventricular map (see “Results”), and second, to examine the change of AT and APD in an isolated Langendorff-perfused heart, in the absence of any alteration of pacing site.

Metabolic and electrophysiologic stability of the preparation was a major prerequisite for this study. Flow, pressure, pH, temperature of the perfusate, and temperature at five to eight epicardial sites were measured at least every 30 minutes. Experiments in which pH was below 7.32, above 7.48, or varied by more than 0.07 and experiments in which temperature varied by more than 0.5°C between any epicardial sites or throughout the experiment were excluded from analysis (n=2). Experiments also were excluded from analysis if premature beats (n=1), atrioventricular block during atrial pacing (n=1), sinus-rhythm interference due to ventriculoatrial block during ventricular pacing (n=1), or sinus frequency higher than the paced frequency occurred (n=3). Before data analysis, the entire set of MAP recordings obtained in a single experiment was assessed for stability and quality. Stable MAP recordings throughout the entire protocol from at least 12 different epicardial sites were required to include an experiment in statistical analysis; this condition was not met in two experiments that were subsequently discarded. These stringent criteria allowed only 11 out of 21 preparations to be submitted to data analysis.

Data Analysis

Monophasic action potentials were analyzed for AT, APD, and RT. AT during atrial pacing was measured from the onset of QRS in the electrocardiogram, to the time when local activation occurs at the ventricular recording site (upstroke of the MAP), and during ventricular pacing from the stimulus spike to the upstroke of the MAP. To compare AT during atrial and ventricular pacing in any given experiment, AT at every single epicardial site was also analyzed as the delay from the site with earliest activation. APD was measured from the intrinsic deflection of the upstroke to the level of 90% repolarization. All data from each site are the average of five consecutive MAP recordings. Local RT was calculated as the sum of AT and APD. The accuracy of the measured intervals was within 2 msec as determined by repeated measurements made by two independent observers. The two-tailed Student’s t test for paired data was used to compare mapping data at different times of the pacing protocol in the same experiment. The degree of heterogeneity of ventricular repolarization (dispersion of RT) was estimated from the coefficient of variance of RT between all recordings obtained in a given heart (minimum number of recordings, 10).

Results

Reproducibility and Stability of AT and APD, and Their Interrelation During Baseline Conditions

Repeated mapping of the right and left ventricle at intervals of 10 minutes, using the drawn diagram of the heart, demonstrated good reproducibility of AT and APD measurements at each of the 12–20 individual recording sites. AT differed between the two consecutive measurements by only 1.0–1.5 msec (1.2±0.2 msec), and APD differed by only 2.1–3.0 msec (2.4±0.3 msec). To assess the electrophysiologic stability of the colloid-perfused isolated heart preparation, constant-rate right atrial pacing was continued for a total of 4 hours and measurements were repeated at 30 and 60 minutes, and at 2, 3, and 4 hours. Throughout this period, MAPs remained stable in amplitude and configuration (Figure 1), and AT measurements at the preselected sites remained constant within 2±2 msec (range, 0–5 msec). APD remained unchanged (average, −0.1 msec) during the first hour of continuous pacing but shortened by an average of 4±3 msec during the second hour. At 3 and 4 hours, mean APD was 11±5 msec and 20±5 msec, respectively, shorter as compared with beginning pacing measurements. The standard deviations of the change in APD from the start of pacing to 4 hours later ranged from 2.0 to 3.8 msec (average, 2.7±0.8 msec),
indicating that APD shortening occurring during control experiments was relatively uniform over the heart (Figure 1).

When APD was plotted as a function of AT, there was a consistent inverse correlation between AT and APD, such that shorter AT was associated with longer APD and vice versa. This relation remained significant throughout the entire right atrial-pacing protocol. Measured at 30 and 60 minutes and then every hour after the start of pacing, the slopes of the linear regression between AT and APD remained within a range of $-1.05$ to $-1.41$, and the range of the corresponding linear-correlation coefficients was $0.71-0.67$ (Table 1). Thus, although slight electrophysiologic deterioration of the preparation occurred during the experiment, these changes were uniform over the ventricular surface.

**Changes in the AT/APD Relation at Various Intervals During Atrial and Ventricular Pacing**

The effect of an alteration in ventricular activation sequence on ventricular repolarization was determined by repeated mapping after a change in pacing site. The first two mapping studies were performed after 30 and 45 minutes of continuous right atrial pacing at a rate of 180 beats/minute. This phase presumably continued the supraventricular activation sequence experienced by the ventricles before explantation. As in the control experiments, APD was inversely correlated to AT with a linear-regression slope of greater than $-1$. In the representative example given in Figure 2 (panel A), the linear-regression slope for the relation between AT and APD at 45 minutes of atrial pacing was $-1.73$ ($r$, $0.87$, $p<0.0001$), indicating that usually a site with later activation repolarized before a site with earlier activation. Five minutes after the switch to ventricular pacing, however, the inverse linear correlation was lost ($S$, $0.16$, $r=0.25$, NS) (panel B). With continuing ventricular pacing, a significant linear and inverse correlation between AT and APD again developed (panels C and D), and the magnitude of the negative slope increased progressively (ventricular pacing for 120 minutes: $S$, $-0.51$, $r=0.73$, $p<0.001$).

Two hours after continuous constant-rate right ventricular pacing was begun, the stimulus output was switched back to the right atrial pacing wires to reestablish the original supraventricular activation sequence. Mapping 5 minutes after resumption of atrial pacing again demonstrated loss of the inverse correlation between AT and APD ($S$, +0.91, $r=0.52$, $p<0.05$). After 60 minutes of atrial pacing, however, a significant inverse correlation was again restored ($S$, $-0.63$, $r=0.56$, $p<0.02$).

Table 2 summarizes the changes in correlation coefficient, and Table 3 summarizes the slope

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**Table 1. Linear-Regression Analysis for Relation Between AT and APD in Control Experiments (n=4)**

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<td>SEM</td>
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<td>0.02</td>
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$r$, correlation coefficient; S, slope.
changes of the linear-regression analysis for the relation between AT and APD at each of the nine mapping studies during the entire pacing protocol. These data confirm the findings in the example shown in Figure 2, that is, immediately after alteration of the ventricular activation sequence, the inverse correlation between AT and APD diminished and only gradually recovered with prolonged pacing from the ectopic site, and the reverse phenomenon occurred when the supraventricular activation sequence was reestablished.

**Cause and Effect in the Changing Correlation Between AT and APD**

Abruptly changing the pacing site from a right atrial to a right ventricular site causes a rapid change in the ventricular activation sequence, but once changed, the ventricular activation sequence should remain stable for as long as the pacing site is kept constant. Accordingly, changes in the linear regression that occurred during the period of pacing at a constant site should reflect changes in APD rather than changes in AT. This was tested by analyzing the degree of change in AT and APD at each of the epicardial mapping sites at the beginning and end of each right atrial and right ventricular pacing period. The data presented in Table 4 confirm that switching the pacing site from right atrial to right ventricular, and vice versa, produced a sudden marked change in the average AT, with relatively little change in average APD, whereas during continuing pacing from either the right atrium or right ventricle, only APD underwent progressive, significant change, and AT remained essentially constant. These data indicate that the progressive increase in the negative slope and the improvement of the correlation coefficient of the linear regression analysis between AT and APD during prolonged alterations in activation sequence cannot be explained by changes in AT but are caused by a slow adaptation of APD to the altered activation sequence.

Figure 3 further illustrates the slow time course with which APD at two different sites (sites A and B) changed when the activation sequence was abruptly altered. Altering the activation sequence by switching to right ventricular pacing lengthened the AT at site A (left ventricular, midseptal) by 17 msec and shortened it at site B (right ventricular, basal) by 4 msec. Changes in AT occurred immedi-
Table 2. Correlation Coefficients From Linear-Regression Analysis for Relation Between AT and APD During Changes in Ventricular Activation Sequence (n=9)

<table>
<thead>
<tr>
<th>Rabbit</th>
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<tr>
<td>SEM</td>
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*p<0.05 versus 45 min atrial pacing; †p<0.05 versus 5 min ventricular pacing; ‡p<0.05 versus 120 min ventricular pacing; §p<0.05 versus 5 min second atrial pacing.

Ately after the change from atrial to ventricular pacing, and once changed, AT remained constant as long as the pacing site was kept constant. In contrast, changes in APD developed very slowly over the ensuing 120 minutes of constant right ventricular pacing. There was a gradual, small increase in APD at site B, which had undergone a small decrease in AT, and there was a slow but more pronounced decrease in APD at site A, which had undergone a greater increase in AT. When, after 120 minutes of ventricular pacing, pacing was switched back to the atrium, AT at sites A and B immediately returned to values very similar to those occurring during the original supraventricular activation sequence. In contrast, APD at both sites changed very slowly and in a direction opposite to that measured during the previous, reverse change in activation sequence.

Effect of APD Adaptation on Dispersion of Ventricular Repolarization

An inverse correlation between AT and APD should make RT more uniform within the heart. Figure 4 summarizes the changes in the coefficient of RT variance, used as an estimate of repolarization dispersion at the beginning and end of each right atrial and right ventricular pacing period, averaged from all nine experiments. Immediately after the switch to ventricular pacing, the variability of RT among the mapping sites markedly increased, indicating that the loss of the inverse correlation between AT and APD leaves the repolarization sequence in a less organized, more dispersed state. With continuing pacing from the same right ventricular site, variability of RT decreased significantly, increased again when right atrial pacing was resumed, and again diminished with continued right atrial pacing. As seen by comparison (Figure 4 and Table 3), a decrease in dispersion parallels an improvement in the inverse correlation between AT and APD.

Discussion

This study presents several intriguing findings. The first is the inverse correlation between AT and...

Table 3. Slopes From Linear-Regression Analysis for Relation Between AT and APD During Changes in Ventricular Activation Sequence (n=9)

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*p<0.05 versus 45 min atrial pacing; †p<0.05 versus 5 min ventricular pacing; ‡p<0.05 versus 120 min ventricular pacing; §p<0.05 versus 5 min second atrial pacing.
Anterior atrial pacing

Site A
ATatr. pac. = 16 ms
ATvtr. pac. = 12 ms

Site B
ATatr. pac. = 16 ms
ATvtr. pac. = 12 ms

FIGURE 3. Upper panel: Epicardial surface diagram with recording sites A (left ventricular, midseptal) and B (right ventricular, basal). Switch in pacing site from atrial to ventricular pacing caused lengthening of activation time (AT) at site A and shortening at site B. Lower panel: Slow time course of adaptation of action potential duration (APD) to sudden change in AT after switch in pacing site. (For further explanation, see text.)

TABLE 4. Average Change in Activation Time (AT) and Action Potential Duration (APD) During Right Atrial–Right Ventricular–Right Atrial Pacing Protocol

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<td>19±9</td>
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</tbody>
</table>

A, change from end of first atrial pacing to 5 min after the onset of right ventricular pacing; B, change from 5 min to 120 min of continuous ventricular pacing; C, change from 120 min of ventricular pacing to 5 min of second atrial pacing; D, change from 5 to 60 min of continuous second atrial pacing. Change is measured in absolute terms. Data are expressed in msec±SD. Each average is based on data from a total of 124 epicardial sites (nine experiments, each 10 to 18 sites).

FIGURE 4. Bar graph of coefficient of variance of repolarization time (RT) at various times of pacing protocol. Data represent mean from nine experiments.

APD in ventricles that are depolarized along their normal supraventricular activation pathway. The second more intriguing finding is that the inverse relation between AT and APD appears to be the result of a very slow mechanism that conditions ventricular repolarization according to the sequence of ventricular activation. If ectopic ventricular pacing is sustained long enough, APD adjusts to the new activation sequence in such a way as to correlate again with AT in an inverse fashion. Thus, the opposing direction of activation and repolarization sequence, which is the basis of the normal concordant T wave, does not seem to be an a priori relation but is acquired by the heart during constant activation sequence.

An inverse relation between AT and indexes of repolarization has been reported previously from isolated and in vivo canine heart studies and for both the endocardial and epicardial surface of the human heart. The significance of this inverse relation is that it helps explain the concordance of
the T wave. In the human heart, the slope of this inverse correlation averaged −1.32, which corresponds well with the relation between AT and APD in the present isolated rabbit heart study; during the initial atrial pacing phase, the average linear-regression slope was −1.63. Similar to humans, the rabbit body surface electrocardiogram has a concordant T wave consistent with an inverse relation between depolarizing and repolarizing electrical forces.

Mechanisms of Activation-Dependent Modulation of Repolarization

A mechanism proposed to explain the effect of activation sequence on APD or repolarization is electrotonic interaction. Studies in isolated ventricular muscle and Purkinje fiber preparations have shown that repolarizing (anodal) currents applied during repolarization shorten the action potential and that depolarizing (cathodal) currents applied during repolarization prolong the action potential. Because electrotonic interaction is a passive electrical phenomenon with only minimal (capacitative) delay, this mechanism cannot alone be responsible for the slowly developing and persistent effects on repolarization. One therefore has to postulate another factor that modulates (strengthens or weakens) the degree of electrotonic interaction between myocardial cells. Cardiac cells are electrically coupled by intercellular gap junctions that provide low resistance pathways. It is conceivable that repeated current flow in the same direction through these junctions may decrease their resistance even further, thereby amplifying the electrotonic effect. If conditioning of cellular electrical communication through repeated, uniform use is indeed responsible for the slow modulation of repolarization (and its retention), myocardium can be thought to possess some form of rudimentary “memory.” Further basic investigation is needed to identify the cellular or molecular basis of this previously unrecognized form of intercellular communication in the heart.

Study Limitations

This study has several limitations. First, because recordings were made only from the epicardium, we could not assess the influence of transmural activation on the epicardial APD. Second, differences in AT between different epicardial sites of the rabbit heart were relatively small, which is not surprising considering that the entire rabbit ventricle is depolarized in less than 20 msec. Although we attempted to “perfect” our analysis of MAP recordings by using high-speed recordings and stringent criteria for determining the onset of local activation and repolarization, the short time frame within which the rabbit ventricle depolarizes probably increased the “noise level” of our data. Third, the overall observation period in our preparations was limited to a maximum of 4 hours. Slight but progressive shortening of APD in the isolated rabbit heart preparation prevented us from extending the recording period. The clinical study of Rosenbaum et al.2 showed that pacing-induced primary T wave changes require 24–48 hours to fully develop, and that an even longer time of normal activation sequence is required for them to disappear. It is possible that the development of the inverse relation between depolarization and repolarization would have progressed even farther (steepening its slope and improving its correlation coefficient), if pacing could have been continued for longer times in our Langendorff heart preparation.

Clinical Implications

The dependence of APD on activation sequence, and the long time required to establish such close correlation, has several important implications. An inverse correlation between AT and APD tends to compensate for the successive delay along the ventricular activation pathway and, consequently, tends to synchronize ventricular repolarization. Concomitant with this postulate, we found less dispersion of repolarization after prolonged pacing from the same site, when the inverse correlation between AT and APD was highly significant, than we found shortly after a change in ventricular activation sequence, when the inverse correlation disappeared. Accordingly, a heart that is activated along the same activation pathway for a long time (as is the normal heart with supraventricular impulse origin and conduction over the His-Purkinje system) can be expected to have a more synchronized global repolarization of the ventricular myocardium than a heart shortly after a change in activation sequence, as in ventricular extrasystoles or short runs of ventricular tachycardia. By the same rationale, the short bursts of ventricular pacing commonly used during electrophysiologic testing would perturb the natural synchrony of ventricular repolarization. The resulting increase in dispersion of ventricular repolarization could add to the arrhythmia propensity of the ventricles.

The activation sequence–dependent modulation of ventricular repolarization may explain electrocardiographic repolarization abnormalities after a period of aberrant conduction or ectopic activity. Patients with intermittent left bundle branch block often demonstrate T wave inversion on resumption of a normal ventricular excitation, and this persistent T wave change may reflect adaptation of ventricular APD to the previous aberrant conduction pattern. Similarly, patients with ventricular preexcitation,1,27 tachycardia,8,9 and repeated uniform extrasystoles10,27,29 may demonstrate T wave changes long after normalization of their rhythm. Our study suggests that, contrary to previous contentsions, these fascinating phenomena are based on a physiologic property of the myocardium and do not necessarily imply pathophysiologic conditions such as ischemia, autonomic reflex alterations, or pacing-induced myocardial injury.
Finally, as already implied by Rosenbaum and coworkers,5,27 our study suggests that accumulation and retention of repolarization changes dictated by the activation sequence plays a dominant role in the creation of the ventricular gradient. Secondary T wave changes, formerly believed to be simply a reflection of an abnormal activation sequence without changes in APD, thus may not be limited to the period of abnormal activation but may also involve changes in APD, provided that abnormal activation lasts long enough to condition these changes. Accordingly, a dogmatic categorization of T wave changes into “primary” and “secondary” can no longer be upheld.

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References
3. Wilson FN, MacLeod AG, Barker PS, Johnston FD: The determination and the significance of the areas of the ventricular deflections of the electrocardiogram. Am Heart J 1934;10:46–61

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A Costard-Jäckle, B Goetsch, M Antz and M R Franz

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