Initial and Secondary ST-T Alternans During Acute Myocardial Ischemia in the In-Situ Pig Heart

Ichiro Watanabe, MD and Leonard S. Gettes, MD

Summary
The factors responsible for the ST-T wave alternans (STTA) and associated arrhythmias during acute ischemia have not been clarified.

In acutely ischemic porcine myocardium, we recorded transmural unipolar and bipolar electrocardiograms and mid-myocardial extracellular K+ ([K+]e) from the center of the ischemic zone during 8-minute episodes of ischemia. Two different STTAs occurred. The initial STTA, which occurred at 4 minutes 15 seconds ± 12 seconds of ischemia during sinus rhythm, was most prominent in the subendocardium, independent of [K+]e and activation block, and heart rate dependent. It occurred in 13/19 (68%) occlusions at heart rates ≤ 100 bpm and in 22/23 (96%) at > 100 bpm. The second STTA was more obvious and greatest in the subepicardium. It began in the later phase of ischemia and was also heart rate dependent (5/19 [26%] occlusions at heart rates ≤ 100 bpm and 10/23 [44%] at > 100 bpm). This STTA was consistently associated with 2:1 change in the bipolar electrogram morphology, possibly due to 2:1 conduction block. Ventricular fibrillation (VF) occurred only at > 100 bpm.

The initial STTA may be independent of conduction abnormalities and represent primary repolarization alternans. The second STTA may be secondary to and indicative of 2:1 activation block or marked alternans of the action potential amplitude/duration. The associated VF most likely reflects the underlying conduction abnormality. (Int Heart J 2016; 57: 327-335)

Key words: Extracellular K+, Action potential, Ventricular fibrillation

Waveforms of extracellular unipolar electrograms recorded from acutely ischemic myocardium show an increased R wave amplitude, TQ segment depression, ST segment elevation, and T wave inversion.

These changes are related to disparities between normal and ischemic myocardium in the transmembrane action potential amplitude and duration, to activation delay in the ischemic zone, or to both. Beat-to-beat alternation of the unipolar waveform is also observed. This electrical alternans could be caused by change in the transmembrane action potential configuration, alternation in the degree of activation delay, or both. Another possibility, suggested by Hellerstein and Liebow, is that ST segment alternans occurs when certain fractions of the ischemic myocardium fail to respond on alternate beats - that is, in association with 2:1 block.

Thus, it remains unclear whether electrical alternans in this setting is related to changes in the transmembrane action potential configuration, to activation delay, or to partial 2:1 block. The relation needs clarification because several authors have suggested that the appearance of electrical alternans is associated with the onset of ventricular arrhythmias. The study described herein was conducted to determine whether the development of electrical alternans in ischemic porcine myocardium is related to changes in action potential configuration, to changes in the activation sequence, or to both and to determine the effect of heart rate on the incidences of electrical alternans and ventricular fibrillation (VF).

METHODS

Experimental preparation: The care of animals used in this study conformed to the Position of the American Heart Association on Research Animal Use and was conducted in accordance with accepted guidelines for the care and treatment of experimental animals at the University of North Carolina. Approval was obtained from the University of North Carolina at Chapel Hill’s Institutional Animal Use and Care Committee. The experimental preparation was similar to the preparation that we reported previously (Figure 1). Twenty-two domestic swine of either sex and weighing 30–50 kg were anesthetized with sodium pentobarbital (25 mg/kg), and this was followed by α-chloralose, as needed. Mechanical ventilation and supplemental oxygen were supplied via an endotracheal tube and a Harvard respirator. Arterial blood gases were monitored,
and appropriate ventilator adjustments were made to maintain arterial PO2 > 80 mmHg and a pH of 7.35–7.45. Catheters were placed in the femoral artery for blood pressure monitoring and blood sampling and in the femoral vein for blood sampling and administration of fluids and drugs. Core temperature was continuously monitored with a temperature probe (Yellow Springs Instrument Co., Yellow Springs, OH, USA). Heating blankets were used to maintain the animals’ body temperature at 36–37°C. The heart was exposed via median sternotomy and free of branches was selected for cannulation and dissected from surrounding tissue. The epicardial margin between ischemic and non-ischemic tissues was identified by brief occlusion of the vessel at this site, and 4–6 groups of ion-selective/unipolar and bipolar electrodes were placed at various locations in the center of the ischemic zone, defined as the region > 10 mm inside the visible cyanotic border, and in the normal (non-ischemic) zone.

After electrode placement, systematic heparin (10,000 U followed by 2,000 U/hour) was administered. A carotid artery-to-LAD shunt was created as previously described for later intracoronary administration of drugs. Placement of the shunt in the LAD took approximately 2–3 minutes, but the shunt flow was stopped for 5 minutes because successive occlusions produced similar metabolic and electrical changes. To ensure that all preparations were alike with respect to the duration of ischemia during shunt placement, ischemia was maintained for a total of 5 minutes during shunt placement in each case. Perfusion of the distal LAD via the shunt was maintained at 1.2 mL/kg body weight/min, which has been shown previously to provide a flow of 1.2–1.5 mL/g/heart tissue/minute. Atrial pacing was used to increase heart rate. Arterial blood pressure and the lead II electrocardiogram were recorded continuously during each experiment with a 12-channel Graphtec Linearcorder (Graphtec, Yokohama, Kanagawa, Japan).

**Ion-selective electrodes:** Ion-selective plunge electrodes were fashioned and calibrated by methods described previously. Briefly, 1 end of a Teflon-coated silver wire (0.007 in diameter) was chloridized by soaking it in sodium hypochlorite. K+-sensitive electrodes were made by covering the sponge with a polyvinylchloride-valinomycin-based membrane. Reference electrodes were fashioned in an analogous manner but lacked the ion-selective membrane. Two K+-selective electrodes along with 2 reference electrodes for recording unipolar and bipolar electrograms constituted 1 electrode group. Electrodes were calibrated before each experiment in standard solution (3 and 10 mmol/L KCl). Only electrodes that showed baseline stability to < 1 mV/hour drift and 95–105% of the predicted Nernstian slope (56- to 62-mV shift per decade change in K+ activity at room temperature) were used. After electrode insertion, in-vivo performance of the K+ electrodes was tested by methods described previously. At the end of each experiment, the electrodes were removed from the heart and re-tested in vitro to confirm stable function throughout the experiment. The group of electrodes was threaded into a 19-gauge hypodermic needle, which was used to insert the electrodes into the mid-myocardium to a depth of 4–6 mm. The needle was then withdrawn, leaving the electrodes embedded in the myocardium. Up to 6 electrode groups were used in each experiment.

**Transmural electrodes:** In 7 experiments, transmural distribution of ST-T wave alternans (STTA) was determined by inserting 1 or 2 5-pole needle electrodes at the center of the ischemic zone. The 5-pole needle electrode consists of 5 electrodes placed at an interelectrode distance of 2 mm, allowing the recording of 5 unipolar DC electrograms (0–500 Hz) and 4 bipolar electrograms (50–500 Hz) from 2 adjacent electrode sites.

**Microelectrodes:** In 5 experiments, transmembrane action potentials from subepicardial tissue layers were recorded with micropipettes, each with a flexible, long tip. The micropipettes were pulled with a standard microelectrode puller and filled with 3M KCl solution. Tip resistance was between 15 MΩ and 35 MΩ. The electrode was mounted on a tungsten wire (diameter, 0.002 inches). The wire was connected to a high-input resistance buffer amplifier. A reference electrode made of silver/silver chloride wire was placed as close as possible to the microelectrode. Signals were differentially DC-amplified, continuously monitored on an oscilloscope, and recorded on a Graphtec Linearcorder at a paper feed speed of 50 mm/second.

**Experimental protocol:** Fifty minutes after cannulation of the LAD, the first in a series of myocardial ischemias of 8 minutes duration was induced by the abrupt cessation of flow through the LAD shunt during sinus rhythm. Mean sinus rhythm heart rate was 98 ± 4 bpm. In 13 experiments, the second ischemia of 8 minutes duration was induced during sinus rhythm after 50 minutes of reperfusion. In 9 experiments, right atrial pacing was performed at 30 bpm to approximately 50 bpm higher than the sinus rhythm rate, and the second myocardial ischemia of 8 minutes was induced after 50 minutes of reperfusion.

**Data collection and analysis:** The amplified signals from all electrodes, along with a lead II electrocardiogram, were digitized (Phoenix Data analog-to-digital converter) and simultaneously sampled (1000 samples per second) every 15 seconds during myocardial ischemia by a MicroVAX II/GPX computer (Digital Equipment Corporation, Maynard, MA, USA). Extracellular K+ ([K+]e) values were calculated from measured millivolt changes according to the calibration curve of each electrode and the systemic [K+]e determined from the arterial blood sample obtained immediately before the event. An activity co-
efficient of 0.746 was used in calculating the $[K^+]_e$ concentration. Signals from bipolar electrograms were filtered between 50 Hz and 500 Hz, and signals from unipolar electrograms were DC-coupled to a common reference placed in the aortic root. Local activation was taken as the peak of the high frequency deflection on the local bipolar electrogram. Activation delay at each time point was calculated individually for each electrode by subtracting the baseline activation time (as referenced to an electrode in the nonischemic zone) from that at each time point. Local activation block was defined as the absence of a local activation spike of at least 1 mV. Only sinus (or atrial paced) beats were analyzed. The number of acceptable electrodes in each experiment ranged from 3–5 for $[K^+]_e$.

Local activation was taken only from the needles in which an acceptable K$^+$-sensitive electrode was included. Action potential duration (APD) was measured manually at 90% (APD$_{90}$) repolarization.

**Statistical analysis:** Data are presented as the mean ± SEM unless otherwise indicated. Statistical analysis was performed by the Mann-Whitney U test or Fisher’s exact test, as appropriate. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered significant.

![Figure 2](image_url)

**Figure 2.** A: Subepicardial transmembrane action potentials, mid-myocardial unipolar direct current (DC) electrograms, and bipolar electrograms recorded before (control, left) and during 2 minutes 15 seconds (middle) and 3 minutes 15 seconds (right) of acute ischemia. Action potential duration alternans and unipolar ST-T alternans were observed at 3 minutes 15 seconds of ischemia. Note that there is no 2:1 activation block or 2:1 change in the bipolar electrogram shape at the time of STTA. $[K^+]_e$ indicates extracellular K$^+$; ECG, lead II surface electrocardiogram; AP, epicardial transmembrane action potential; and APD$_{90}$, action potential duration at 90% repolarization. 90% repolarization time of the epicardial transmembrane action potential.

B: Recordings of unipolar direct current (DC) and bipolar electrograms from mid-myocardium at the center of the ischemic zone. Left panel shows unipolar and bipolar electrograms before acute ischemia. The initial ST-T alternans (STTA, middle) consists of alternans of the ST-T segment of the unipolar DC electrogram and is not associated with beat-to-beat changes in activation delay or configuration of the bipolar electrogram. The secondary STTA (right) consists of marked alternans of the ST-T segment of the unipolar DC electrogram and is associated with 2:1 activation block in the bipolar electrogram. K$^+$, indicates extracellular K$^+$. 

RESULTS

A total of 42 coronary artery occlusions were studied in 22 pigs.

Two STTAs: STTA of the unipolar DC electrograms from reference electrodes placed in the mid-myocardium of ischemic myocardium occurred at 4 minutes 36 seconds ± 29 seconds of ischemia at a spontaneous heart rate ≤ 100 bpm (96 ± 4 beats/minute, n = 6) and at 4 minutes 18 ± 19 seconds at a spontaneous heart rate > 100 bpm (127 ± 5, n = 11, P < 0.001). The corresponding [K+]e concentrations were 7.9 ± 0.7 mM and 6.6 ± 0.3 mM, and activation delays were 34 ± 6 ms and 24 ± 4 ms, respectively. There was no statistically significant difference in the STTA onset time (P = 0.725), [K+]e concentration (P = 0.056), or activation delay (P = 0.063) at the onset of STTA between heart rates ≤ 100 bpm and > 100 bpm. Representative experiments are shown in Figure 2. In the experiments shown, the unipolar DC electrogram, bipolar electrogram, and [K+]e were recorded from the same electrode group. The initial STTA was not associated with changes in bipolar electrogram configuration but was associated with alternans of the subepicardial transmembrane action potential (Figure 2A). However, unlike the initial STTA (Figure 2B, middle), the second, more obvious STTA was associated with 2:1 conduction block or marked alternans of the action potential amplitude/duration, as evidenced on the bipolar electrogram (Figure 2B, right). In another experiment, STTA became more obvious when the local bipolar electrogram changed shape (Figure 3). The unipolar DC electrograms in Figure 3 were obtained at 15-second intervals after cessation of coronary flow, and the local conduction delays measured from bipolar electrograms from the same electrode group are given. The initial STTA occurred 2 minutes 45 seconds after the onset of ischemia. STTA became more obvious as the ischemia progressed, and the greatest STTA was observed between 4 minutes and 5 minutes after the onset of ischemia. Local bipolar electrograms at 4 minutes of ischemia (open triangle) alternated in shape. After 5 minutes of ischemia, the STTA became small in amplitude and then disappeared. On unipolar DC electrograms recorded at 5 minutes 30 seconds of ischemia, no STTA was observed (open square), and no alternation in the shape of the bipolar electrograms was observed despite the progression of ischemia shown by the continuous increase in [K+]e (Figure 3). Thus, we speculated that the initial STTA as primary repolarization alternans, independent of conduction abnormalities and the second, more obvious STTA as secondary to and indicative of 2:1 change in the activation pattern or activation block.

Transmural distribution of STTA: In 2 of 7 experiments in which transmural DC electrograms were recorded, the initial STTA was observed only in the subendocardial electrograms, and in the other 5 experiments, the initial STTA was observed transmurally but the STTA was greater in the subendocardial recordings. A representative experiment is shown in Figure 4. In this experiment, the initial STTA was observed in the subendocardial recordings (closed and open triangles) at 3 minutes 23 seconds of ischemia. To clarify the existence of STTA in subendocardial recordings (Figure 4, middle A, B), 2 consecutive beats were made to overlap each other. No STTA was observed in the subepicardial recordings (Figure 4, middle, D, E). At 4 minutes of ischemia, STTA was observed transmurally; however, the degree of alternation was greater in the subepicardial electrograms (Figure 4, right, D, E) and was associated with 2:1 conduction block or marked alternans of the activation sequence evidenced by the bipolar electrogram from the subepicardial myocardium (Figure 4, right, bipolar electrogram, D, E).

Effect of heart rate on the incidences of STTA and VF: The relation between heart rate and the incidences of STTA and VF was evaluated in 42 coronary occlusions. Representative experiments are shown in Figures 5 and 6. In the experiment shown in Figure 5, no STTA in the transmural unipolar electrograms and no alternans of subepicardial action potentials were observed during the 8 minutes of ischemia at a heart rate of 81 bpm (Figure 5, left), whereas STTA and action potential alternans appeared at 3 minutes 15 seconds of ischemia at a heart rate of 130 bpm (Figure 5, right), although the increase in [K+]e was similar between the 2 heart rates (Figure 5). The initial STTA (3 minutes 45 seconds of ischemia at a heart rate of 130 bpm, Figure 5, right) was observed at a [K+]e concentration lower than that at 8 minutes of ischemia at a heart rate of 81 bpm (Figure 5, left). The increase in [K+]e during ischemia was similar between a heart rate of 90 bpm and a heart rate of 140 bpm (Figure 6, left); however, ventricular fibrillation de-

Figure 3. Unipolar direct current (DC) electrograms recorded every 15 seconds during ischemia. Note that STTA begins at 2 minutes 45 seconds of ischemia (closed and open triangles), and at 4 minutes of ischemia, the ST-T alternans (STTA) is associated with beat-to-beat changes in the bipolar electrogram shape. At 5 minutes 30 seconds of ischemia, STTA disappeared despite an increase in [K+]e, which coincided with disappearance of beat-to-beat changes in bipolar electrogram shape. K', indicates extracellular K'.
Marked ST-T alternans (STTA) in the subepicardial electrograms and alternans of the subepicardial action potentials were observed before the development of VF (Figure 6, right). The effect of different heart rates (sinus rhythm [98 ± 4 beats/min] and atrial paced rhythm [143 ± 3 beats/minute, \( P < 0.001 \)]) on the incidence of initial STTA was 5/9 (56%) and 9/9 (100%, \( P = 0.041 \)), and initial + secondary STTA was 1/8 (13%) and 4/8.
Thus, we divided pigs into 2 groups based on heart rate (≤ 100 bpm and > 100 bpm, Table I). At heart rates ≤ 100 bpm, the initial STTA occurred in 8 of 19 cases (42%), and in 5 of 19 (26%), there was a second STTA. At heart rates > 100 bpm, the initial STTA occurred in 22 of 23 cases (96%) and in 10 cases (44%), there was a second STTA. The incidences of initial STTA and VF were higher at heart rates > 100 bpm than at heart rates ≤ 100 bpm (P = 0.025 and P < 0.002, respectively). Ventricular fibrillation occurred only at > 100 bpm (P < 0.001) and in only 9 of 23 (39%) occlusions. All hearts with VF had an initial STTA, but only 5 of 9 (56%) had a secondary STTA (Table II).

**Table I.** Initial and Secondary STTA and VF Per Heart Rate

<table>
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<tr>
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<th>HR ≤ 100 bpm</th>
<th>HR &gt; 100 bpm</th>
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<tbody>
<tr>
<td>Initial STTA</td>
<td>8 (42%)</td>
<td>22 (96%)</td>
</tr>
<tr>
<td>Initial &amp; secondary STTA</td>
<td>5 (26%)</td>
<td>10 (44%)</td>
</tr>
<tr>
<td>VF present</td>
<td>0 (0%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>STTA –</td>
<td>N/A</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>STTA +</td>
<td>N/A</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Initial STTA only</td>
<td>N/A</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Initial &amp; secondary STTA</td>
<td>N/A</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>VF absent</td>
<td>19 (100%)</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>STTA –</td>
<td>6 (32%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>STTA +</td>
<td>13 (68%)</td>
<td>13 (93%)</td>
</tr>
<tr>
<td>Initial STTA only</td>
<td>8 (42%)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Initial &amp; secondary STTA</td>
<td>5 (26%)</td>
<td>5 (36%)</td>
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STTA indicates ST-T wave alternans; VF, ventricular fibrillation; –, not present; and +, present. *P = 0.025 versus HR ≤ 100 bpm; †P = 0.002 versus HR ≤ 100 bpm.

**Table II.** Occurrence Versus Non-Occurrence of STTA and Its Characteristics in Cases of VF Versus No VF During Acute Myocardial Ischemia

<table>
<thead>
<tr>
<th></th>
<th>VF not present</th>
<th>VF present</th>
</tr>
</thead>
<tbody>
<tr>
<td>STTA –</td>
<td>7 (21%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>STTA +</td>
<td>26 (79%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Initial only</td>
<td>16 (49%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Initial &amp; secondary</td>
<td>10 (30%)</td>
<td>5 (56%)</td>
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</table>

STTA indicates ST-T wave alternans; VF, ventricular fibrillation; –, not present; and +, present.

**Discussion**

Since the early description of electrical alternans by Lewis,16 several hundred cases have been reported in association with an apparently disparate set of clinical and experimental conditions. Hellerstein and Liebow19 were the first to suggest, on the basis of their studies in animals in 1950, that repolarization alternans is mechanistically linked to arrhythmogenesis in the setting of acute ischemia. A pilot study by Smith, et al19 raised the possibility that alternans may also be a marker of vulnerability to clinical arrhythmias. The objective of our study was to investigate whether alternans of the ST segment and T wave in acutely ischemic porcine myocardium was related to beat-to-beat alternation of action potential configuration or to alternation in the activation sequence or to 2:1 block.

**Properties of electrical alternans during ischemia:** We found 2 STTAs. The initial STTA that occurred 4 minutes 15 ± 12 seconds after the onset of ischemia was most prominent in the
subendocardium, was independent of activation block, and was heart rate dependent. It occurred in 68% of occlusions at rates < 100 bpm and in 96% of occlusions at rates > 101 bpm. [K+]e was 7.1 ± 0.3 mM and activation delay was 28 ± 4 msec at the onset of STTA. The secondary STTA was more obvious with and greatest in the subepicardium. It began 4–8 minutes after the onset of ischemia and 30 to approximately 60 seconds after the onset of the initial STTA. This secondary STTA was also heart rate dependent (26% of 19 occlusions at < 100 bpm and 44% of 23 occlusions at > 101 bpm) and was consistently associated with a change in the shape of the bipolar electrogram or observance of 2:1 conduction block.

Possible mechanisms of electrical alternans during ischemia: Initial STTA during ischemia Green, et al[19] reported that during acute ischemia, the STTA was greatest in the endocardium during the first 4–6 minutes and at 6–8 minutes, the STTA was greatest in the epicardium. In an earlier reported study, isochronal maps of local excitation detected on 61 unipolar electrograms revealed that STTA correlated poorly with activation delay and that there was no change in the activation sequence. Our study results support the notion that the initial STTA is related to changes in the action potential configuration rather than to changes in the activation sequence. Dilly and Lab[10] suggested 2 possible mechanisms for the action potential alternans during ischemia. The first possibility involves change in the electrical restitution. Under non-ischemic conditions, the action potential duration increases monotonically with an increase in the diastolic interval after the proceeding action potential.[21] The short diastolic interval preceding beat one results in incomplete deactivation of an outward current and incomplete recovery of the slow inward current. Therefore, the first action potential has a short duration. The diastolic interval preceding the second action potential will be longer than that preceding the first one, and the action potential prolonged. This in turn will result in a shorter diastolic interval and reduced duration of the third action potential. The recovery process could be slowed by ischemia, resulting in flattening of the electrical restitution curve with depression of the plateau of the curves, therefore, STTA could occur spontaneously in the ischemic area.[14] Sudden prolongation of the cardiac cycle length is known to eliminate action potential duration alternans within a few beats.[18,19] Both hypoxic and acidic perfusion have been shown to cause an increase in action potential duration alternans and marked persistence of the phenomenon.[30] One possible mechanism for change in electrical restitution during ischemia might be a decrease in conductance of inwardly rectifying K+ channels,[21-23] resulting in an increase in action potential duration beyond that expected from the increase in [K+]e during ischemia.[24] The second possibility involves change in intracellular calcium cycling. Change in intracellular calcium cycling would affect the action potential by influencing calcium currents, calcium-activated currents,[24,25] and electrogenic sodium-calcium exchange.[27] Acute ischemia has been shown to increase the systolic and diastolic levels of the calcium transients and to cause a pattern of intracellular calcium alternans associated with alternans in the duration of monophasic action potentials.[26] Verapamil and diltiazem, which are calcium antagonists, and caffeine, which is a sarcoplasmic reticulum inhibitor of calcium, have been shown to prevent or greatly delay action potential duration and STTA.[28-31]

Secondary STTA during ischemia Downar, et al[32] reported that marked STTA coincided with 2:1 responses of action potential during acute ischemia in the intact porcine heart, and this was often followed by ventricular arrhythmia. Using 61 unipolar electrograms recorded from the epicardial surface, Carson, et al[33] observed that STTAs with and without 2:1 conduction block occurred simultaneously in acutely ischemic myocardium. STTA in the absence of 2:1 block was similar to the STTA we observed in the subendocardium (Figure 5, middle), and STTA with 2:1 conduction block was similar to the STTA we observed in the subepicardium (Figure 5, right). Furthermore, we observed that STTA coincided with 2:1 changes in the local bipolar electrogram waveform (Figure 4). In the experiment shown in Figure 4, STTA disappeared in association with disappearance of 2:1 changes in the local bipolar electrogram waveform, although the ischemia progressed. Fleet, et al demonstrated that transient recovery of local activation in the center of the ischemic myocardium during 10 minutes of LAD occlusion,[34] and Gettes, et al showed that activation delay in the center of the ischemic myocardium was improved,[35] and they speculated the mechanism(s) as 1) an increase in the upstroke of slow channel dependent cells, 2) a hyperpolarizing effect on cells with depressed resting membrane potential resulting in a secondary increase in the upstroke velocity of the action potential presumably through the rapid sodium dependent channel, and 3) a lessening of ischemia induced uncoupling of cellular elements. An explanation for STTA with 2:1 changes in the local bipolar electrogram waveform was proposed by Sutton, et al[36] who considered more than 1 pathway for local conduction. If 1 pathway shows 1:1 conduction and another pathway shows alternation between complete block and delayed conduction, the action potential of delayed conduction is limited by the refractory period of the conducted beat and thus generates no propagating beat but rather an electrotonic deflection during the plateau phase.

Electrical alternans and arrhythmias Dilly and Lab[30] reported rate dependence of action potential duration alternans in ischemic myocardium. Increased pacing rates inevitably cause greater metabolic demand on the myocardium and thus augment ischemic stress. However, Kurz, et al[37] reported instantaneous discontinuation of action potential duration alternans after a major increase in cycle length. In our experiments, STTA did not coincide with an increase in [K+]e, (Figure 6). Thus, cycle length appears to have an independent effect on the generation of electrical alternans and is functionally separate from its effect on ischemic burden. We found the incidence of initial STTA and VF to be significantly higher at heart rates > 100 bpm (Table I). However, the initial STTA was observed without VF in 42% (Table I). The secondary STTA was observed in 44% of cases at > 100 bpm and in only 56% of cases ofVF, an incidence that did not differ significantly from that in cases without VF (Table I, Table II). Hope, et al[38] showed fast heart rates during acute ischemia to be associated with acceleration in the time course of ischemic zone epicardial activation delay and early ventricular tachycardia. Previous experiments conducted in our laboratory[39] have also shown rate-dependent activation delay but a rate-independent increase in [K+]e during acute myocardial ischemia. We speculate that the lower incidence of secondary STTA in our experiments derives from the fact that we recorded [K+]e, and the unipolar DC electrograms from the mid-myocardium, which, in comparison to the epicardium, produced less activation delay or block that would
cause a second STTA (Figures 4–6) and/or from the fact that we recorded only a limited number of electrograms; other site(s) of ischemic myocardium might show a secondary STTA. Sutton et al.17 showed that alternans might be localized to small areas and, as such, by virtue of the recording technique, might have been underestimated in the group as a whole. In addition, Carson, et al.18 showed the existence of initial and secondary STTAs in the neighboring ischemic regions. Janse, et al.19 showed that ventricular premature beats usually followed deep negative T waves in ischemic myocardium, when "injury" currents across the ischemic border were maximal, and the earliest activity always occurred at the normal zone where Purkinje activity was recorded. They concluded, therefore, that 2 mechanisms are responsible for the very early ischemic arrhythmias: a "focal" mechanism located on the normal side of the ischemic border, possibly induced by injury currents in normal Purkinje fibers and a mechanism involving macro- and micro-reentry in the ischemic myocardium. In their experiments, STTAs were often preceded by ventricular premature beats.

Study limitation: In this in-vivo study, the zero line of the DC electrogram and transmembrane action potential could not be demonstrated because of drifting of the baseline. Further, we did not perform detailed intramyocardial and/or epicardial mapping and therefore could not demonstrate that beat-by-beat changes in unipolar and bipolar electrogram morphology in the setting of secondary STTA were due to 2:1 conduction block, 2:1 alteration in the direction of conduction, or 2:1 change in the marked action potential amplitude and/or duration.

Conclusions: Our experiments provide evidence that STTA is a distinct electrophysiologic characteristic of ischemic myocardium and that 2 mechanisms contribute to the alternans: 1) the initial STTA may be independent of conduction abnormalities and represent primary repolarization alternans; and 2) the second, more obvious STTA, may be secondary to and indicative of 2:1 activation block somewhere in the ischemic zone.

DISCLOSURE

Conflict of interests: None

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