Discordant S-T alternans contributes to formation of reentry: a possible mechanism of reperfusion arrhythmia

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Tachibana, Hidetada, Isao Kubota, Michiyasu Yamaki, Tetsu Watanabe, and Hitonobu Tomoike. Discordant S-T alternans contributes to formation of reentry: a possible mechanism of reperfusion arrhythmia. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H116–H121, 1998.—Although a relationship between S-T alternans and life-threatening arrhythmia has been recognized, the mechanism is poorly understood. We examine the role of S-T alternans in the occurrence of ventricular fibrillation (VF) after reperfusion. The left anterior descending coronary artery was occluded for 20 min and then abruptly reperfused in 12 intravenously anesthetized open-chest dogs. Twenty unipolar epicardial electrograms were recorded during the control state, at the end of occlusion, and after reperfusion. The largest magnitude of S-T alternans among 60 leads was defined as the maximum S-T alternans. Isochronal maps of activation time in paced beat and spontaneous ventricular premature contractions (VPC) were analyzed. After reperfusion, VF ensued in six dogs. The maximum S-T alternans increased progressively and then almost disappeared within 90 min of coronary reperfusion. The left anterior descending coronary artery was ligated for 20 min and was reperfused abruptly. Each recording was repeated during the control state, at the end of occlusion, and immediately after reperfusion. We recorded the beginning of VF after reperfusion with repeated recordings (success rate: 5/6). One dog was excluded from the following analysis because VF occurred during 20 min of coronary occlusion.

Surgical preparation. This study conformed to the guiding principles of animal experiments in our institution. Thirteen mongrel dogs (13–21 kg) were anesthetized with an intravenous administration of 30 mg/kg pentobarbital sodium. Under positive-pressure ventilation with room air supplemented with oxygen (3–5 l/min), the thorax was opened in the fifth intercostal space, the pericardium was opened, and a pericardial cradle was made to support the heart at an appropriate position. Arterial pressure, blood gases, and pH were monitored. The Po2, PCO2, and pH of the arterial blood were maintained within the physiological range. The sinus node was crushed, and the right atrium was paced at a cycle length of 400 ms.

Mapping of epicardial electrograms. The heart was wrapped in an array of 60 unipolar electrodes (14, 15). These electrodes were made of fine silver wires (0.005-in. diameter) that were insulated except at the point of attachment. The electrode array had 6 rows and 10 columns (15). The interelectrode distance was 7–10 mm. All recording electrodes were referenced to a Wilson’s central terminal. Data were digitized at a sampling frequency of 1,000 Hz using a multichannel data-recording system (CD-G015, Chunichi Denshi, Nagoya, Japan) (11). We can record electrograms for 4 s at voluntary timing with this system. The data were stored on a magneto-optical disk.

Experimental protocol. The left anterior descending coronary artery was ligated for 20 min and was reperfused abruptly. Each recording was repeated during the control state, at the end of occlusion, and immediately after reperfusion. We recorded the beginning of VF after reperfusion with repeated recordings (success rate: 5/6). One dog was excluded from the following analysis because VF occurred during 20 min of coronary occlusion.

Measurements. The flat portion of the P-R segment was defined as zero level. The amplitude of the S-T segment was measured at 40 ms from the J point, and the S-T elevation was defined when the level exceeded 1 mV. The magnitude of S-T alternans was derived as the difference in the level of the S-T segment and T wave was common in patients with increased risk for ventricular arrhythmias. However, the mechanism by which S-T alternans causes VF remains poorly understood.

The phenomenon of S-T alternans has frequently been noted in the presence of myocardial ischemia (2, 4, 12, 20). The magnitude of S-T alternans temporally associates with the occurrence of ventricular fibrillation (VF) (4, 20), especially during the reperfusion phase (2, 5, 18). Several reports speculated that generation of excitatory current (1, 12, 13) or reentrant circuit by S-T alternans caused VF (5, 20). Recently, Rosenbaum et al. (19) reported that electrical alternans affecting the S-T segment and T wave was common in patients with increased risk for ventricular arrhythmias. Moreover, the mechanism by which S-T alternans causes VF remains poorly understood.

Previously, we have demonstrated that the risk of VF increases when the magnitude of S-T alternans increases, especially when the S-T alternans is discordant (1, i.e., the S-T changes in the adjacent leads are out of phase) during acute myocardial ischemia in dogs (14). Because S-T alternans reflects the alteration of action potential duration (3, 13, 20), a discordant appearance of the S-T alternans may indicate spatial inhomogeneity in action potentials. Therefore, we hypothesized that, around the area of discordant S-T alternans, conduction was blocked and a reentrant circuit was formed, facilitating the occurrence of VF. The goal of the present study was to elucidate, by use of the mapping of epicardial electrograms in dog hearts, a correlation between the spatial distribution of S-T alternans and subsequent VF after coronary reperfusion.

METHODS

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Because there is no accurate way to distinguish very slow conduction from conduction block, we arbitrarily decided that possible conduction block occurred when the difference in activation time between two adjacent leads was >50 ms during a single cardiac cycle (6).

Statistical analysis. Mann-Whitney’s U test was used to compare values between groups with and without VF. Wilcoxon matched-pairs ranks test was used to compare values before and after reperfusion. Quantitative data were expressed by means ± SD. Differences were considered significant at $P < 0.05$.

**RESULTS**

VF was observed in 6 of 12 dogs (VF group), and the average onset of VF was at 42 ± 26 s after reperfusion. The other six dogs did not show VF 2 h after reperfusion (non-VF group). In all of the non-VF group, we verified that S-T elevation recovered to baseline.

S-T elevation and S-T alternans in VF and non-VF groups. The number of leads showing S-T elevation, the maximal level of S-T elevation, and the maximal magnitude of S-T alternans (maximum S-T alternans) before and after reperfusion are summarized in Table 1. There were no significant differences in number of leads showing S-T elevation or in maximal S-T elevation between the VF and non-VF groups either before or after reperfusion. There was also no significant difference in maximum S-T alternans before reperfusion between VF and non-VF groups. The maximum S-T alternans of the VF group was significantly greater than that of the non-VF group after reperfusion (6.9 ± 4.8 vs. 1.6 ± 0.2 mV, $P < 0.01$). Figure 1 shows the time course of maximum S-T alternans after reperfusion. Maximum S-T alternans in ventricular fibrillation (VF) group (A) increased rapidly, but those in the non-VF group (B) did not show a rapid increase.

S-T alternans and activation sequence of VPC after reperfusion. We could evaluate the activation sequence of ventricular premature contractions (VPC) after reperfusion in five dogs for each group by use of isochronal maps. Figure 2 shows the S-T alternans and activation sequence at both atrial pacing and VPC in representative cases of the VF group (dog C, Fig. 2A) and the non-VF group (dog H, Fig. 2B) after reperfusion. In the isochronal map of Fig. 2A, top right, the relationship between open and closed circles indicated discordant S-T alternans. In Fig. 2A, the isochronal map during atrial pacing showed no conduction block. However, the

<table>
<thead>
<tr>
<th>Dog</th>
<th>During Coronary Occlusion*</th>
<th>After Reperfusion†</th>
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<tbody>
<tr>
<td></td>
<td>No. of elevated S-T leads</td>
<td>Max S-T elevation, mV</td>
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<tr>
<td>VF group</td>
<td></td>
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</tr>
<tr>
<td>A</td>
<td>18</td>
<td>17.4</td>
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<td>B</td>
<td>33</td>
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<td>Mean ± SD</td>
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<tr>
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<tr>
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<td>24</td>
<td>23.6</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>22.8 ± 3.3</td>
<td>18.9 ± 4.9</td>
</tr>
</tbody>
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No. of elevated S-T leads refers to number of leads with S-T segment elevation >1.0 mV. VF, ventricular fibrillation; Max, maximal. *Data at end of coronary occlusion; †data when maximal magnitude of S-T alternans became largest during 60 s after reperfusion. Significant differences: ‡$P < 0.01$ vs. non-VF group; §$P < 0.05$ vs. before reperfusion.
Fig. 2. S-T alternans and activation sequence of atrial pacing and ventricular premature contractions (VPC) in representative cases of VF group (A) and non-VF group (B). Display format is an apical polar projection of ventricles with left ventricular apex in center. Isochronal lines are drawn every 10 ms, and gray zone show area of S-T elevation above 1 mV. *Earliest activation in each contraction (time 5). Circles in isochronal maps at top right of A and B indicate leads with S-T alternans above 0.5 mV in last 2 paced electrograms (waves 1 and 2) before onset of VPC. Open circles, S-T level of wave 1 is larger than that of wave 2. Filled circles, S-T level of wave 2 is larger than that of wave 1. Between site of open and filled circles was discordant S-T alternans, as shown in electrograms of A. A: a case of VF group (dog C). Isochronal maps at center show VPC that resulted in VF. Earliest activation of first beat of VPC (VPC1) appeared in lead A1. Wavefront circulated around both ends of conduction block (presented by heavy bold line), coalesced, and reached distal side of block at 70-ms isochrone. Lead of earliest activation of following beat (VPC2) was F1 (activation time 181 ms), and activation sequence was similar to VPC1. These isochronal maps suggested that reentrant circuit was formed. As illustrated in isochronal map at right, site of conduction block was located between sites with discordant S-T alternans. B: a case of non-VF group (dog H). Activation of VPC (isochronal map at center), which occurred at 21 s after reperfusion, did not show conduction block. At right, isochronal map showed that S-T alternans was concordant.
VPC that occurred at 18 s after reperfusion (VPC1) resulted in a functional conduction block between leads E1 and F1 (represented by heavy solid line). The activation wavefront circulated around both ends of the block, coalesced, and reached the distal side of the block at 70-ms isochrone. The lead of the earliest activation of VPC2 was located on F1 (activation time was 181 ms, where time 0 was the earliest activation of VPC1), and the activation sequence was similar to that in VPC1. These isochronal maps suggested that a reentrant circuit was formed. This activation led to ventricular tachycardia (VT), and VF occurred after VF continued for several seconds. The activation sequences in VT beats were also similar to those in VPC2. As illustrated by the isochronal map in Fig. 2A, top right, the conduction block was seen between sites with discordant S-T alternans. The earliest activation of VPC1 was consistent with the border of the S-T elevation area but not with the location of S-T alternans.

In a case of the non-VF group (dog H), a single VPC occurred at 21 s after reperfusion. Conduction block was not observed during atrial pacing or on that VPC (Fig. 2B). As the isochronal map in Fig. 2B, top right, indicates, discordant S-T alternans was not observed in this dog. The earliest activation of the VPC was not consistent with a site of S-T alternans. Of the other four dogs in the non-VF group, only one had a correlation between the location of S-T alternans and the earliest activation of VPC.

Figure 3 shows the activation sequence of the VPC that resulted in VF in the remaining four dogs of the VF group. Figure 3 is displayed in the same format as Fig. 2. In dog B, the earliest activation appeared on lead B1; however, another activation initiated on D5 30 ms later than the first activation. In two of four dogs (dogs B and E), the VPC originated from the area with S-T alternans, where conduction block occurred. In these dogs, the activation circulated around both ends of the block, coalesced, and reached the distal side of the block at the 150-ms (dog B) or 170-ms isochrone (dog E). The earliest activation of the following spontaneous beats was located on the proximal site of the block in both dogs. These maps suggested that a reentrant circuit was formed. After the same type of reentrant tachycardia was maintained for several seconds, the VT degenerated into VF. The conduction block was consistent with the border of a discordant S-T alternans. Dog D and dog F did not show conduction block; however, the maximal difference of activation time in adjacent leads, which was illustrated by a white line, was located between sites with discordant S-T alternans in each dog. In these dogs, the earliest activation of the following beat was initiated from the border between the ischemic and the nonischemic area. In the non-VF group, the activation sequence of VPC after reperfusion showed that the maximal difference of activation time in adjacent leads was <30 ms (mean 22.5 ± 5 ms).

**DISCUSSION**

In the VF group, the magnitude of maximum S-T alternans progressed with time until VF occurred. The activation sequence of the VPC in three dogs of the VF group indicated that the conduction was blocked between sites with discordant S-T alternans. The activation sequence after the VPC suggested that a reentrant circuit was formed.

S-T elevation and alternans in reperfusion arrhythmia. There were no differences in the extent (i.e., number of leads with S-T segment elevation) or magnitude of maximum S-T alternans progression.
tude of S-T segment elevation between VF and non-VF groups either before or after reperfusion. The lack of correspondence between S-T segment changes and the propensity for VF was previously reported during ischemia (14) and after reperfusion (18). These data suggested that the level of S-T elevation during coronary occlusion or after reperfusion was not always a good predictor of VF. In accord with several reports (2, 5, 14, 18), we observed that the increase of magnitude and discordant appearance in S-T alternans, not S-T level, was a sensitive sign for reperfusion-induced VF.

Mechanism of S-T alternans. Although the mechanisms of S-T alternans are still unclear, the following possible mechanisms have been discussed: 1) calcium load, 2) chemical products, and 3) 5-HT receptor.

Increase in calcium levels in ischemic myocardium is a well-known phenomenon (23). Because the S-T alternans during coronary occlusion was attenuated by the administration of calcium antagonists (8, 16), calcium overload may be responsible for the appearance of S-T alternans. Washout chemical products from the ischemic myocardium also are postulated to induce S-T alternans after reperfusion (22). Hirata et al. (9) reported that acidic perfusion increased electrical alternans. The products that affected intra- and extracellular pH may also contribute to augment S-T alternans after reperfusion. Recently, it was reported that nesopamil, a calcium channel and 5-HT2 receptor blocker, attenuated T-wave alternans during and after coronary occlusion rather than diltiazem (17). This result suggested that S-HT2 receptors may also contribute to electrical alternans.

Activation sequence of VPC. The analysis of the activation sequence of VPC in the VF group demonstrated that the local conduction block along the boundary of discordant S-T alternans induced VF. As shown in the isochronal maps in Fig. 2A and Fig. 3, the depolarization wavefront of VPC spread via the circulation around the conduction block and reached the distal side and then reactivated the proximal side of the block. These activation sequences suggested that reentry was formed. S-T alternans has been shown to be associated with alternans of action potential duration (APD) (3, 13, 20, 24) or effective refractory period (ERP) (7) in experimental studies. The border of discordant S-T alternans was supposed to reflect the zone where APD or ERP was drastically changed. These lines of data suggest that a conduction block and reentrant circuit were created by heterogeneity of ventricular repolarization, as shown regionally by discordant S-T alternans.

We used whole heart mapping for the analysis. This technique allowed us to analyze the macroreentry circuit and S-T alternans distribution at the same time. To our knowledge, this is the first report that the border of discordant S-T alternans contributes to the conduction block and reentrant circuit.

Electrophysiological mechanisms of reperfusion arrhythmia and S-T alternans. We found in the present study that the discordant appearance of S-T alternans contributed to the formation of the reentrant circuit during reperfusion. In three dogs of the VF group, the analysis of activation sequences revealed that the reentry was the most probable mechanism for maintaining VT. In the remaining two dogs, the activation sequence of VPC did not show the conduction block and the activation was initiated from the border of ischemic and nonischemic myocardium. Ideker et al. (10) reported that ventricular activation during the transition to VF arose near the border of the ischemic-reperfused region.

Clinical implications. Electrical alternans was regionally specific and was linearly projected to the precordial appearance of S-T alternans (18). Therefore, the monitoring of S-T alternans distribution on precordial leads may be useful for evaluating the vulnerability to VF after coronary reperfusion. Such evaluation of the vulnerability to VF would be helpful in patients with thrombolytic therapy. Prinzmetal’s angina, and spontaneous recanalization of acute myocardial infarction.

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