The QRS complex during transient myocardial ischemia: studies in patients with variant angina pectoris and in a canine preparation

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ABSTRACT We made continuous electrocardiographic recordings on magnetic tape during 15 episodes of ischemia in five patients with variant angina to determine the characteristics of the QRS changes. Orthogonal leads were used and the electrocardiograms were analyzed visually and by digital computer. Changes were quantified by subtracting baseline electrocardiograms from those obtained during ischemia. Large changes in the QRS occurred during ischemia but the waveform quickly returned to baseline when the episode subsided. In all patients there was prolongation of the QRS duration and an increase in QRS voltage during the terminal 40 msec of the waveform in the lead(s) showing the most marked ST displacement. The increase in the terminal QRS could be represented by a vector directed toward the ischemic zone. In a given patient the amplitude of ST displacement varied between episodes, presumably because of variation in the intensity of ischemia, but the QRS changes were directionally similar in each episode. In two patients there was also a smaller change involving the initial 40 msec of the QRS that could be represented by a vector directed away from the ischemic zone. To determine the possible mechanism for the electrocardiographic changes, ischemic episodes of 120 to 150 sec were produced in seven dogs and electrocardiographic recording and analysis techniques similar to those used in patients were employed. Myocardial conduction velocity was measured in three directions in the ischemic zone and was correlated with simultaneous electrocardiographic recordings from the body surface. The electrocardiographic changes in the dog preparation were virtually identical to those in the patients and strongly correlated with a fall in myocardial conduction velocity. We conclude that the QRS changes during variant angina result from the altered excitation pattern produced by conduction delay in the ischemic zone. The probable cause for the increase in terminal QRS voltage is delayed (and uncanceled) activation of the ischemic zone.


WE HAVE investigated the QRS changes during spontaneous ischemia in patients with variant angina by performing a detailed analysis of electrocardiograms from orthogonal leads. To determine the possible explanation for the changes, we have produced transient myocardial ischemia in a dog preparation and have correlated changes in myocardial conduction velocity with the simultaneous electrocardiographic changes that occurred in surface orthogonal leads similar to those that were obtained in the patients.

Methods

Studies in patients. All patients admitted to Vanderbilt Hospital and the VA Medical Center, Nashville, to participate in a research study of vasospastic angina were included in this electrocardiographic study if they consented to continuous electrocardiographic monitoring with special leads and had spontaneous episodes of ischemic chest pain at rest and/or transient ST segment displacement of 0.2 mV or greater. Eight patients met these criteria and in five of these recordings were obtained during 15 episodes of ischemia that were satisfactory for analysis. Records from three patients were excluded for strictly technical reasons such as detached electrodes, signals out of the dynamic range of the recorder, or excessive electrical noise. The electrocardiographic recordings were obtained during an observation period before commencing drug trials. Long-acting nitrates, calcium-channel antagonists, β-adrenoceptor antagonists, and platelet agents were withheld during this phase of the
investigation. Patients were permitted to take 0.4 mg nitroglycerin tablets sublingually when they experienced chest pain. Three of the five patients included in the analysis were men and two were women. Three of the patients had electrocardiographic changes indicative of inferior ischemia and two patients had evidence of anterior ischemia.

Coronary arteriography was performed in all of the patients. One female patient underwent coronary arteriographic examination on three occasions at other institutions before being referred to the Vanderbilt Medical Center for this research study. Multiple views of the coronary arteries were obtained in each study and the vessels were judged to be normal. Two coronary arteriographic studies were performed in the second female patient at a Vanderbilt-affiliated hospital before her referral to our group and no obstructive lesions were noted at the time of either study. These two patients had spontaneous episodes of angina at rest with ST segment elevation and no attempt was made to provoke spasm with ergonovine. One male patient had mild (less than 30% reduction of lumen) lesions in the circumflex, anterior descending, and right coronary arteries. Ergonovine provocation was used during the arteriographic study and there was a further decrease in the caliber of the circumflex artery and the posterior descending artery at the site of the mild lesions. The patient did not experience pain at that time and there was no ST segment displacement. A second male patient had a 35% obstructive lesion in the anterior descending artery that progressed to total occlusion during the arteriographic study. Sublingual nitroglycerin was administered and the obstruction was promptly reduced to its original mild degree. The episode, which lasted approximately 8 min, was associated with chest pain and ST segment displacement. The third male patient had multiple brief episodes of chest pain and ST elevation during the 24 hr recording. Three days after his entry into the study, coronary arteriography was performed and revealed a single, severe obstructive lesion in the anterior descending artery. The patient had chest pain and ST displacement after the initial coronary injection of contrast. A second left coronary injection showed complete occlusion of the anterior descending artery; the vessel reopened after intravenous administration of nitroglycerin.

In the five patients with technically satisfactory electrocardiographic records, the duration of the episodes of ischemia ranged from 3 to 10 min (mean 6 min). In each case the ST segment and the QRS returned to their baseline configurations after the episode of ischemia. The assumption that myocardial necrosis did not occur is based on the brevity of the episodes of ischemia and on the prompt resolution of the electrocardiographic changes.

Electrocardiographic signals from Frank leads X, Y, and Z were continuously recorded on FM magnetic tape in these patients. Episodes of ischemia were identified and segments of the record were digitized at a rate of 256 samples/sec and used for vectorcardiographic analysis or for point-by-point electrocardiographic subtractions. The instantaneous spatial QRS magnitude (QRSSM) was determined at each digitized point during QRS by the equation

$$\text{QRSSM} = \sqrt{(X_{\text{QRS}})^2 + (Y_{\text{QRS}})^2 + (Z_{\text{QRS}})^2}$$  \hspace{1cm} (1)

where $X_{\text{QRS}}$, $Y_{\text{QRS}}$, and $Z_{\text{QRS}}$ are the instantaneous QRS voltages recorded simultaneously from the respective Frank leads. The maximum value of the spatial magnitude during the QRS was taken as the maximum value of QRSSM.

Electrocardiographic subtractions were performed by first visually aligning the onset of the QRSSM waveform generated by equation 1 from baseline data and the waveform obtained similarly with data during peak ischemia. The computer program then performed point-by-point subtractions of voltage values from the X, Y, and Z leads throughout the QRS complex. A waveform QRSSD, representing the magnitude of the difference vector between baseline and ischemia, was then computed by the equation

$$\text{QRSSD} = \sqrt{(1 - B_1)^2 + (1 - B_2)^2 + (1 - B_3)^2}$$  \hspace{1cm} (2)

where the I-B terms represent subtractions of baseline (B) data from ischemic (I) data made at intervals of 4 msec or less throughout QRS complexes from leads X, Y, and Z. We have used a similar method in a previous study to quantify electrocardiographic changes during myocardial infarction.5

Studies in dogs. Seven mongrel dogs weighing between 15 to 22 kg were anesthetized with pentobarbital and a thoracotomy was performed in each. A snare was placed around the left anterior descending artery and pacing wires were attached to the left atrial appendage. To measure myocardial conduction velocity, we developed an electrode array that has a single 0.25 mm silver electrode at the center of a 15 mm Lucite disk. Each of the three bipolar sensing electrodes was in the form of two parallel, 1 mm long silver wires on the surface of the disk. The 0.7 mm spacing of the wires was approximately equal to the width of the depolarization wavefront. The wires were oriented tangentially to an imaginary circle centered about the stimulating electrode to allow the electrode pair to detect the radial passage of the wavefront initiated by the central stimulating electrode. The three electrode pairs, 3 mm from the center and 120 degrees apart, were connected to individual low-noise differential amplifiers and were used to measure myocardial conduction velocity by a method similar to that described by Roberts et al.2 The central electrode was used as a cathodal stimulating electrode and the 12 electrodes mounted on the periphery of the disk 6 mm from the center were anodal electrodes. The electrode connections on the back side of the Lucite disk were encapsulated in epoxy and the entire electrode was sterilized for long-term implantation.

Measurements of conduction velocity were made during atrial pacing and the interval between atrial stimuli was designated $A_1A_3$. The electrogram of the depolarization wavefront initiated by atrial pacing and recorded as it crossed the epicardial electrode array was used to obtain the combined atrial, nodal, His, and myocardial conduction time (CT). The stimulator was programmed to pause for 1 to 2 sec after the twelfth atrial stimulus, and the central ventricular electrode was activated at a time $A_3A_3 + CT$ after the last atrial pacing pulse so that the electrical state of the myocardial region of interest was the same as when the myocardium was activated by a supraventricular source. The electrograms from the radially oriented bipolar pairs were recorded on a seven-channel FM magnetic tape recorder simultaneously with McFee surface leads X, Y, and Z. The bipolar electrograms were digitized at 4096 samples/sec and the surface X, Y, Z signals were digitized at 512 samples/sec. The conduction velocity was determined by measuring the time interval between the stimulus artifact recorded by the bipolar pair and the peak signals from that electrode. Figure 1 shows recordings from the electrode array used to determine myocardial conduction velocity. The stimulus artifact is labeled S. The bipolar electrogram $V_{BP}$ that yielded the highest myocardial conduction velocity, i.e., approximating the longitudinal velocity, is labeled L. The electrogram that yielded the lowest velocity in this example is labeled T for transverse velocity. The time between the onset of the QRS in surface lead Y (not shown in figure 1) and the appearance of the signal in the epicardial electrode during atrial pacing was used as an index of the ventricular activation time.
Results

All five patients with variant angina consistently showed an increase in QRS voltage in leads that showed ST segment displacement during ischemia. The increase in QRS voltage occurred in the last 40 msec of the QRS in all cases. In the two patients with anterior ischemia there was a small change in the initial portion of the QRS that was oppositely directed to changes in the terminal QRS. In figure 2, A, lead Z is shown during a period when the patient was free of signs and symptoms of myocardial ischemia. Figure 2, B is the same lead during spontaneous anterior ischemia and a major change in the configuration of the QRS has occurred, with the initial half of the QRS becoming positive and the terminal portion becoming negative. A slight prolongation of the QRS duration is also seen during ischemia. Variation in the magnitude of QRS changes and ST displacement occurred both

**FIGURE 2.** Data from a patient with variant angina and anterior ischemia. A. Baseline lead Z; B, lead Z during ischemia; C. The difference waveform DZ representing the waveform in B minus the waveform in A. DZL represents the extremum early in the difference waveform for lead Z. DZT represents the extremum late in the difference waveform. The vertical dotted line corresponds to the midpoint of the QRS complex in the QRS♂ waveform at baseline.
between patients and within patients, presumably as a result of variation in the intensity of ischemia. However, the QRS change within a given patient was qualitatively similar during repeated episodes of ischemia. In figure 2, C the baseline electrocardiogram has been subtracted from that obtained during ischemia, yielding the difference shown in this figure. The early and late extrema in the difference waveform are labeled DZ₁ and DZ₄.

To compare the QRS changes between the patients, we then normalized all waveforms by dividing the instantaneous voltage in each lead by the maximum value of QRS₅₀; thus no baseline waveform would have a value greater than 1.0, the normalized maximum value of QRS₅₀. The QRS changes during ischemia were quantified by computing the spatial difference vector relative to the baseline QRS in the three orthogonal leads. Figure 2 shows how the Z component of the difference vector was determined; the other two components were subtracted in a similar manner. The instantaneous magnitude of the spatial difference vector QRS₅₀ is given by equation 2. With the normalization, a QRS₅₀ of zero would mean that the ischemic and baseline QRS vectors were the same at that instant, whereas a QRS₅₀ of 1.0 would mean that the magnitude of the change was equal to 100% of the magnitude of the baseline QRS. The maximum values of QRS₅₀ were 0.45, 0.51, and 0.68 for the three patients with inferior ischemia and 1.12 and 1.42 for the two patients with anterior ischemia. Although these large QRS₅₀ values imply that there were major changes in the QRS complex associated with ischemia, it is of interest to examine the direction of these different vectors before inferring their significance. As shown in figure 3, the maximum value of the normalized difference vector pointed anteriorly in patients with anterior ischemia and inferiorly in those with inferior ischemia.

Although there was a major change in the QRS complex in the particular lead that showed ST displacement, the maximum QRS₅₀ increased by only 9 ± 4% at the peak of ischemia. The existence of a large difference vector QRS₅₀ without significant changes in the QRS₅₀ is consistent with a rotation of the electrical axis of the heart produced by the shift in the timing of the contribution of the myocardium in the ischemic zone. Figure 4 illustrates plots of the amplitude and the relative time at which the peak changes were observed during spontaneous ischemia in the five patients. Figure 4, A shows the changes in the Y lead for the three subjects with inferior ischemia, and figure 4, B shows the changes in the Z lead for the two subjects with anterior ischemia. The onset and offset of the baseline QRS₅₀ waveform were used to define relative times 0.0 and 1.0, respectively, in the QRS complex to account for differing QRS durations between subjects. The coordinates of the points in the figure correspond to the normalized amplitude and relative time of the extrema in the difference waveform for a particular lead. For example, the peak in figure 2, C is the early extremum in the Z lead difference waveform and is labeled DZ₁, while the later minimum is labeled DZ₄. After the amplitudes of these two points were normalized to the maximum QRS₅₀ at baseline and the times were converted to relative times, their coordinates were (0.27, 0.31) and (0.69, -1.06), respectively, as plotted in figure 4, B. The vertical broken lines in figure 2, C and figure 4 correspond to the midpoint of the QRS complex, i.e., relative time 0.5. It can be seen

![FIGURE 3](http://circ.ahajournals.org/)

**FIGURE 3.** The magnitude and direction of the maximum instantaneous difference vector in the frontal (A) and horizontal (B) planes during variant angina in the five patients. Values are normalized to baseline maximum QRS₅₀. Vectors A, B, and C are from the patients with inferior ischemia and vectors D and E are from patients with anterior ischemia. In each case the difference vector points toward the area of ischemia.
FIGURE 4. A, The relative time of occurrence in the QRS complex and the normalized magnitudes of the extrema of the difference waveforms in lead Y for patients with inferior ischemia. B, The same plot as in A for the difference waveforms in lead Z for patients with anterior ischemia.

from figure 4, B that the early changes in the QRS during anterior ischemia were directed away from the ischemic zone while the late changes were directed toward it. This is consistent with the maximum changes shown earlier in figure 3. The late differences in figure 4 represent a change from an average QRS amplitude in the lead shown of 0.51 ± 0.26 at baseline to 0.81 ± 0.13 at peak ischemia (p < .01).

Animal studies. A representative electrocardiogram obtained at peak ischemia is shown in figure 5. In panel A the baseline electrocardiogram in the X lead is shown, panel B shows the electrocardiogram during maximum ischemia, and panel C is the result of the subtraction of the baseline electrocardiogram from that obtained at maximum ischemia. There is no significant early extremum in this case. The directions of the maximum difference vectors, QRS$_{SD}$, are illustrated in figure 6. The vectors are directed anterolaterally, which is consistent with ischemia in the area supplied by the left anterior descending artery. By the same method of analysis used for the human subjects, we found that for the animals, the average value of the (normalized) QRS$_{SD}$ was 0.65 ± 0.34. The relative time of the maximum change in lead X is shown in figure 7, A. In the dog preparation, as in the patients, the electrocardiographic changes are predominantly in the latter portion of the QRS. An early QRS change that could be represented by a vector pointing away from the area of ischemia occurred in four of the five dogs and this was also seen in patients with anterior ischemia. In these four dogs these changes were seen primarily in lead Z, as shown in figure 7, B.

The time course of QRS changes during ischemia is illustrated in figure 8, A, which is a plot of the R wave amplitude in lead X normalized to QRS$_{SM}$. The R wave amplitude increased from 0.41 ± 0.22 to 0.73 ± 0.23 (p < .001) at peak ischemia. All of the QRS changes rapidly resolved after the coronary arterial snare was released. Since the maximum QRS$_{SM}$ did not appear to vary with time, an analysis of variance was performed that showed significant differences between animals [F(4,32) = 127.8, p < .01], but no significant differences between time points [F(8,32) = 1.04, p = .43].

Changes in conduction velocity during ischemia. The conduction time from the central stimulating electrode to each of the radial bipolar electrodes was measured and the conduction velocity was calculated. Since conduction velocity is influenced by myocardial fiber orientation, we determined the maximum and minimum conduction velocity in each animal. The maximum velocity is assumed to approximate conduction veloc-

FIGURE 5. A dog with anterior ischemia induced by transient occlusion of the left anterior descending artery. A, Baseline lead X; B, lead X during ischemia; C, A difference waveform obtained by subtracting waveform in A from that in B. DX$_{E}$ and DX$_{L}$ represent early and late extrema in the difference waveform. Note that the major changes occur late in the QRS.
ity parallel to the fiber orientation and is labeled longitudinal velocity and the minimum velocity approximates the conduction velocity perpendicular to the fibers and is termed transverse velocity. The electrode positions were labeled at autopsy and fiber direction was determined by a cardiac pathologist with no knowledge of the conduction velocity measurements. In four dogs the alignment of the electrode was within 20 degrees of a line parallel with the fiber and in each case this electrode displayed the most rapid conduction velocity. In three cases the fibers were sufficiently curved to preclude exact measurement of an angle, but the most rapid velocity was still in the direction of the fibers.

In the five animals with an electrode in the left anterior descending distribution the mean longitudinal velocity was 59.9 ± 10.8 cm/sec, the transverse velocity was 23.1 ± 3.6 cm/sec, and the ventricular activation time 27.3 ± 2.8 msec at baseline. Although a slight increase in conduction velocity was noted in most dogs during the initial 30 sec of ischemia, this change was not statistically significant. As ischemia continued there was marked slowing of the longitudinal and transverse myocardial conduction velocity, as shown graphically in figure 8, B and tabulated in table

FIGURE 6. The magnitude and direction of the instantaneous difference vector, QRS$_{SD}$, in the frontal (A) and horizontal (B) planes during transient occlusion of the left anterior descending artery in five dogs. The values are normalized to baseline QRS$_{SM}$

FIGURE 7. The relative time of occurrence in the QRS complex and the magnitudes of the normalized extrema of the difference waveforms. A. Lead X; B. Lead Z. In one dog there were no significant changes in lead Z.

FIGURE 8. A. The time course of the R wave amplitude in lead X during transient occlusion of the left anterior descending artery in a dog. The R wave amplitude was normalized to baseline QRS$_{SM}$. B. The conduction velocity and ventricular activation time as a function of time. Note that maximum ventricular activation time and minimum conduction velocities occur at the time of maximum ischemia.
DIAGNOSTIC METHODS—ANGINA

TABLE 1
Time course of parameters of change in QRS and conduction velocity in the ischemic zone during transient snare occlusion in five dogs

<table>
<thead>
<tr>
<th>Time relative to coronary ligation (sec)</th>
<th>-30</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized R-lead X</td>
<td>0.42</td>
<td>0.41</td>
<td>0.34</td>
<td>0.55</td>
<td>0.66</td>
<td>0.72</td>
<td>0.73</td>
<td>0.43</td>
<td>0.42</td>
</tr>
<tr>
<td>± 0.22</td>
<td>± 0.22</td>
<td>± 0.23</td>
<td>± 0.21</td>
<td>± 0.21</td>
<td>± 0.20</td>
<td>± 0.23</td>
<td>± 0.30</td>
<td>± 0.25</td>
<td>± 0.26</td>
</tr>
<tr>
<td>Normalized maximum QRS &lt;sub&gt;sm&lt;/sub&gt;</td>
<td>0.94</td>
<td>1.00</td>
<td>0.94</td>
<td>0.99</td>
<td>1.00</td>
<td>1.02</td>
<td>1.01</td>
<td>0.95</td>
<td>0.93</td>
</tr>
<tr>
<td>± 0.12</td>
<td>± 0.12</td>
<td>± 0.14</td>
<td>± 0.13</td>
<td>± 0.15</td>
<td>± 0.17</td>
<td>± 0.18</td>
<td>± 0.06</td>
<td>± 0.11</td>
<td></td>
</tr>
<tr>
<td>Ventricular activation time (msec)</td>
<td>± 3.5</td>
<td>± 2.9</td>
<td>± 3.0</td>
<td>± 5.7</td>
<td>± 6.4</td>
<td>± 5.8</td>
<td>± 7.2</td>
<td>± 5.8</td>
<td>± 4.7</td>
</tr>
<tr>
<td>Longitudinal velocity (cm/sec)</td>
<td>± 11.0</td>
<td>± 10.8</td>
<td>± 11.1</td>
<td>± 12.7</td>
<td>± 13.0</td>
<td>± 13.4</td>
<td>± 12.9</td>
<td>± 17.2</td>
<td>± 9.8</td>
</tr>
<tr>
<td>Transverse velocity (cm/sec)</td>
<td>± 3.6</td>
<td>± 3.6</td>
<td>± 4.5</td>
<td>± 6.0</td>
<td>± 4.1</td>
<td>± 1.0</td>
<td>± 1.3</td>
<td>± 6.2</td>
<td>± 3.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD (n = 5).
R-lead X = R wave amplitude in lead X normalized to baseline maximum QRS <sub>sm</sub>.

1. The greatest slowing of conduction occurred at the peak of ischemia and ventricular depolarization extended well into the ST segment. Mean longitudinal velocity slowed to 29.5 ± 13.5 cm/sec (p < .005) and transverse velocity slowed to 9.9 ± 1.6 cm/sec (p < .005) at peak ischemia. The longitudinal and transverse conduction velocity rapidly returned to the baseline level after the snare was released. Changes in the ventricular activation time paralleled changes in conduction velocity and the peak time occurred just before the snare was released, as shown in figure 8, B. Ventricular activation time increased from 27.3 ± 2.8 msec at baseline to 40.0 ± 9.0 (p < .02) at peak ischemia. By design, the ischemic zone was in the distribution of the left anterior descending artery in all the dogs. Lead X shows the most marked ST elevation and this lead was used to correlate QRS changes with conduction velocity. The relationship between the R wave amplitude in lead X, the conduction velocity, and ventricular activation time for the five dogs with the electrode in the left anterior descending distribution was assessed and correlation coefficients are given in table 2. There was a strong positive correlation between ventricular activation time and the R wave amplitude in lead X and a negative correlation between R wave amplitude and conduction velocity. The ventricular activation time had a higher correlation coefficient than the conduction velocity measurements. However, the ventricular activation time correlated strongly with the longitudinal and transverse conduction velocities in the ischemic zone (r = −.98 and −.95, respectively). This suggests that 90% to 96% of the variation in the ventricular activation time can be accounted for by the variation in the conduction velocities in the ischemic region. The high correlation between the longitudinal and transverse velocities (r = .97) is also evident in figure 8, B.

Table 9, A shows the baseline Y lead of the electrocardiogram along with the QRS <sub>sm</sub> waveform calculated with equation 1. The three signals from the bipolar electrode are superimposed and are labeled A, B, and C. The signals from the electrode array occurred late in QRS, as is expected when an epicardial electrode is used. Figure 9, B shows the same signals recorded during peak ischemia. Note that the epicardial signals are even later in the QRS, which is indicative of slowed propagation through the ischemic myocardium. The QRS complex is markedly prolonged as compared with baseline, and contributions from the ischemic region are seen where the QRS complex merges into the ST segment.

In two dogs the recording electrodes were placed in the circumflex distribution and ischemia was produced by occluding the anterior descending artery in the same way as in the other animals. The R wave amplitude in

Table 2
Correlations between parameters of conduction velocity and R wave amplitude in lead X during transient coronary occlusion in the dog

<table>
<thead>
<tr>
<th>Correlation coefficient</th>
<th>Ventricular activation time</th>
<th>Longitudinal velocity</th>
<th>Transverse velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>.89</td>
<td>.81</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>F(15)</td>
<td>19.1</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>p value</td>
<td>.01</td>
<td>.05</td>
<td>.05</td>
</tr>
</tbody>
</table>

Measurements were made at seven points in time in the five dogs with radial electrodes in the region supplied by the left anterior descending artery.
lead X increased in these animals, but there was no fall in conduction velocity in this normal myocardial zone (table 3).

**Discussion**

The electrocardiographic changes observed in all five patients during multiple episodes of spontaneous myocardial ischemia of the variant or Prinzmetal type has consistently been an increase in the QRS amplitude in the leads that show the most marked ST segment displacement. If the polarity of the lead is such that a positive ST segment displacement is present, the polarity of the QRS increase is positive. The maximum change occurs in the terminal 40 msec of the QRS and there is an increase in the QRS duration. In some patients a small change is noted in the initial 40 msec of the QRS and this change is electrically opposite to the change observed late in the QRS. Vector analysis of the QRS shows that there is only a small change in the maximum spatial QRS vector magnitude, but there are major changes in the terminal QRS vector that vary with the location of the myocardial ischemia. Inferior wall ischemia produces a difference vector that points anteriorly. When transient myocardial ischemia was produced in a dog preparation, virtually identical QRS changes were noted. Conduction time measurements made simultaneously with electrocardiographic recordings showed that peak QRS changes correlated highly with a fall in conduction velocity and an increase in ventricular activation time. Changes in conduction velocity were not seen in areas of the myocardium remote to the ischemic zone during snare occlusion.

Holland and Brooks\(^1\) used an epicardial electrode to demonstrate delayed ventricular activation during myocardial ischemia in an open-chest pig preparation and related this to increasing epicardial R wave amplitude. David et al.\(^4\) used a partially closed-chest dog preparation to relate increasing endocardial to epicardial conduction times to increasing R wave amplitude. In both of these studies delayed ventricular activation was demonstrated, but conduction velocity in the ischemic zone was not measured. Since the direction of propagation of normal activation depends on the conduction properties and configuration of the Purkinje system located on the endocardial surface and the orientation of the muscle fibers within the myocardium, it is not valid to assume that the time difference between wave fronts recorded on the endocardium and epicardium is a measurement of myocardial conduction velocity. Such measurements give the component of the average conduction velocity along a line connecting the two measurement points, and this velocity may be substantially less than the actual velocity vector. The potential for similar error is inherent in any index of conduction velocity based on measurement between two distant electrodes whether they are both on the epicardial surface or if one is on the epicardium and the other is a remote electrode.

In general, a three-dimensional electrode array is required to obtain the orthogonal components of the velocity vector and, since conduction velocity is influenced by fiber orientation,\(^2\)\(^,\)\(^3\)\(^,\)\(^5\)\(^,\)\(^6\) it is essential to measure velocity both parallel and perpendicular to the muscle bundles. Since the fibers are parallel to the epicardial surface, it should be possible to accurately measure myocardial conduction velocity with properly oriented electrodes on the epicardium if the site of stimulation is also on the epicardium.\(^6\) In our study the radial electrode from which the minimum conduction velocity was obtained should have been within 30 degrees of perpendicular to the fiber direction and the electrode exhibiting the maximum velocity should have been within the same limit for parallel alignment. Roberts et al.\(^2\) plotted the conduction velocity as a
TABLE 3
Time course of parameters of change in QRS and conduction velocity in the nonischemic zone during transient snare occlusion in two dogs

<table>
<thead>
<tr>
<th>Time with respect to coronary ligation (sec)</th>
<th>Coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-30</td>
<td>0</td>
</tr>
<tr>
<td>R-lead X (mV)</td>
<td></td>
</tr>
<tr>
<td>Dog 1</td>
<td>0.56</td>
</tr>
<tr>
<td>Dog 2</td>
<td>1.57</td>
</tr>
<tr>
<td>Ventricular activation time (msec)</td>
<td></td>
</tr>
<tr>
<td>Dog 1</td>
<td>26.3</td>
</tr>
<tr>
<td>Dog 2</td>
<td>18.8</td>
</tr>
<tr>
<td>Longitudinal conduction velocity (cm/sec)</td>
<td></td>
</tr>
<tr>
<td>Dog 1</td>
<td>61.7</td>
</tr>
<tr>
<td>Dog 2</td>
<td>70.9</td>
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<tr>
<td>Transverse conduction velocity (cm/sec)</td>
<td></td>
</tr>
<tr>
<td>Dog 1</td>
<td>28.6</td>
</tr>
<tr>
<td>Dog 2</td>
<td>24.4</td>
</tr>
</tbody>
</table>

R-lead X = maximum R wave voltage in lead X.

function of the angle from the fiber direction. If we utilized the maximum and minimum velocities measured as estimates of the longitudinal and transverse myocardial conduction velocities, the data of Roberts et al.2 can be used to show that the error in an individual measurement of longitudinal velocity could be 25% in the worst case, but the average error should be less than 6%. Similarly, the transverse velocity measurements should be accurate to within 10% for the worst case and 5% on the average. The values we recorded at baseline are remarkably close to those for normal myocardium reported by Roberts et al.2 Despite the similarity, we recognize that imprecise alignment of the electrodes with the myocardial fibers was a potential source of error and the influence of subjacent, nonparallel fibers on net conduction velocity was not measured by this method. These limitations of the technique notwithstanding, our data clearly show that the maximum and minimum conduction velocities measured with the electrode array decreased markedly in the ischemic zone and the changes in conduction velocity were temporally related to changes in the surface electrocardiogram.

Our study also differs from those reported previously in that we made continuous magnetic tape records in patients with variant angina and a detailed electrocardiographic analysis of orthogonal lead data was performed. Similar recording techniques were used in dogs during an intervention that was designed to simulate spontaneously occurring myocardial ischemia in patients. In a similar dog preparation, David et al.4 noted a large increase in the spatial vector magnitude after 150 sec of occlusion. We noted major changes in the R wave of a given lead with an occlusion of this duration, but there was only a small change in the magnitude of the maximum spatial QRS vector in patients and no significant change in this vector magnitude in the dogs. The apparently conflicting findings may be related to differences in the technique of calculating the spatial QRS vector. In our study the spatial QRS magnitude QRS<sub>SM</sub> was calculated throughout QRS from simultaneous X, Y, and Z signals and the maximum value was determined. This maximum value will not always correspond to the square root of the sum of the squares of the maximum QRS amplitude in each orthogonal lead because the maximum value in each of the three leads may occur at different times.

Our observations that some patients have changes in the early part of the QRS that can be represented by a vector that points away from the ischemic zone and that all patients studied have a more marked change affecting the late portion of the QRS are consistent with earlier reports in which either Q waves or increases in R waves were noted.7-10 It is generally accepted that the QRS changes that typically occur in an established transmural myocardial infarction are the result of the failure of infarcted myocardium to contribute to the excitation front. Thus, the potentials at electrode sites overlying large transmural infarcts are dominated by fields generated by boundary zones in the opposite wall that have the capability of depolarizing. Our study demonstrates that conduction velocity...
and the excitation front are slowed but not eliminated in the ischemic zone. This marked slowing of the excitation front may produce relatively uncanceled late wave fronts in the ischemic zone. Thus, the discordant early and late QRS changes may represent an early “hole” in the activation front followed by a late, unopposed contribution from the ischemic zone.

It is known that left ventricular volume increases with myocardial ischemia and that increased intracavitary volume can, in itself, cause an increase in QRS voltage (Brody effect).\(^{11}\) Nelson et al.\(^{12}\) have shown that as the resistivity of intracavitary blood is lowered or as its quantity is increased the strength of radial dipoles is increased and the strength of tangential components is reduced. Cardiac excitation studies by Scher and Young\(^{13}\) and Durrer et al.\(^{14}\) have shown that radially directed dipoles predominate during the initial phases of ventricular depolarization and that the tangential forces are greater in the later phases. Thus, our observation that the later phase of the QRS is increased in a direction opposite to that predicted from Brody’s analysis suggests that this mechanism does not account for the changes observed in our study. Moreover, David et al.\(^{4,15}\) compared the time course of volume changes and QRS changes during acute ischemia and noted that the R wave changes were not in phase with changes in left ventricular volume. Therefore, we are able to infer, but have not rigorously proven, that changes in the pattern of ventricular activation rather than changes in intracavitary volume are the explanation for the electrocardiographic changes seen in individuals with variant angina pectoris.

The predictable relationship between changes in conduction velocity and changes in the surface electrocardiogram during ischemia has implications that extend beyond patients with variant angina. Electrocardiographic methods based on QRS subtraction techniques have been used to estimate infarct size.\(^{1,16–19}\) In animal experiments in which a preinfarct electrocardiogram was used as the reference for the subtraction process, the QRS “difference” correlated highly with the size of the infarction.\(^{16,17}\) In clinical studies in which electrocardiograms obtained early after infarct were used as references the correlation between the QRS difference and infarct size was weaker.\(^{1,18}\) During acute myocardial infarction it is likely that the QRS of the early reference electrocardiogram will be altered by ischemia and subsequent QRS subtractions will yield difference values that include effects from both ischemic and necrotic myocardium. Since the analysis does not delineate the relative contributions of these two processes, the method is of questionable reliability in estimating infarct size.\(^{19,20}\)

In another application, our data lead us to predict that analysis of QRS changes during ischemia will be more accurate in determining the location of ischemia than analysis of ST segment displacement. The ST segment may become displaced in either a positive or negative direction during ischemia, giving rise to ambiguous solutions when the electrocardiogram is used to determine the location of the ischemic zone. For example, ST depression in anterior precordial leads during an acute diaphragmatic myocardial infarction could be a manifestation of ischemic injury of the posterior myocardium resulting from the infarction or could be due to coexisting ischemia of the anterior myocardium. Conduction velocity decreases consistently during severe ischemia, and the analysis of QRS changes as described herein may determine the location of the ischemic zone with greater specificity. Broader clinical applications of the concepts derived from this study are currently being investigated.

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Circulation. 1985;71:901-911
doi: 10.1161/01.CIR.71.5.901

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/71/5/901

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