Relation Between Localization of Coronary Artery Disease and Local Abnormalities in Ventricular Activation During Exercise Tests

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To examine whether or not the location of local abnormalities on body surface isochrone maps reflects the site of myocardial ischemia, 48 coronary artery disease patients without myocardial infarction were studied. Eighty-seven unipolar electrocardiograms distributed over the anterior chest and the back were recorded simultaneously before and after the submaximal treadmill exercise. For each lead, the duration from the QRS onset to the time of the most rapid decrease in QRS voltage was measured (index of ventricular activation [IVA]). Based on the data provided by these 87 leads, IVA isochrone maps (IVA map) in preexercise and in postexercise, as well as IVA maps showing the difference between preexercise and postexercise, were constructed. The IVA was defined as abnormal when it exceeded (mean+2 SD) the normal range. We called the area with the abnormal IVA, the "+2SD area." In patients having a stenosis in the left anterior descending artery, the +2SD area in each map was located mainly on the left anterior chest, whereas in patients having a stenosis in the right coronary artery, the +2SD area in each map was located mainly on the right lower thoracic surface. Moreover, the +2SD area of patients with both left anterior descending and right coronary artery disease appeared on both the left anterior chest and the right lower thoracic surface. In patients with left circumflex artery disease, however, the location of the +2SD area did not suggest a stenotic site because of its small population. On the other hand, it was difficult to determine the ischemic site from the body surface distribution of ST segment depression. The results suggest that local abnormalities on IVA maps have the potential to indicate the ischemic site. The body surface IVA maps can be useful in evaluating the site of myocardial ischemia noninvasively. (Circulation 1990;81:461–469)

Recently, many investigators have reported that ST segment shifts on the surface electrocardiogram (ECG) could not localize myocardial ischemia.1–4 Therefore, there has been a recent interest in the diagnostic value of QRS complex responses to exercise.5–7 Experimental studies indicated that ventricular activation time measured from epicardial electrograms (VAT) increased during acute myocardial ischemia.8–10 The changes in VAT have potential as a new index for myocardial ischemia and for wall motion abnormality caused by myocardial ischemia; but it is clinically difficult to perform epicardial isochrone mapping. On the other hand, isochrone maps constructed from body surface unipolar ECGs are reported to be useful in detecting abnormalities in the ventricular activation sequence.11 We noninvasively constructed body surface isochrone maps of normal volunteers and patients with angina pectoris during exercise test, and examined whether the changes in body surface isochrone maps could localize myocardial ischemia and detect wall motion abnormality.

Methods

Patient Population

From 320 consecutive patients who underwent treadmill exercise testing and by the use of body surface mapping and diagnostic coronary arteriography for the evaluation of chest pain, 48 patients (41 men and seven women), 41–72 years old (mean age, 58.2 years), satisfying all of the following criteria were selected for this study: 1) diagnosis of stable effort angina pectoris; 2) no history of previous myocardial infarction, established by typical chest pain, serum enzyme changes, and ECG findings; 3)
no conduction disturbances such as right bundle branch block, left bundle branch block, or Wolff-Parkinson-White syndrome, and QRS duration of less than 0.12 sec; 4) no clinical or ECG evidence of variant angina pectoris or spontaneous angina at rest; 5) no valvular disease, myocardial disease, or other heart diseases; 6) graded treadmill exercise tests terminated because of moderate or severe angina; 7) no medication with digitalis compounds or diuretics; 8) no wall motion abnormalities such as akinesis or dyskinesis on the left ventriculogram; 9) significant coronary narrowing of 70% or more in the luminal diameter in at least one of the major coronary arteries; and 10) wall thickness of both the interventricular septum and the left ventricular posterior wall, as shown by ECG, less than 13 mm to avoid the influence of hypertrophy. Informed consent was obtained from all patients.

Normal Volunteers

Forty normal volunteers, all men and 22–48 years (mean, 31.9 years old), performed body surface mapping. None of the volunteers had a history of cardiac disorders or systemic arterial hypertension. All had normal physical and ECG reports.

Coronary Arteriography and Left Ventriculography

Selective coronary arteriographic studies were done in multiple projections according to the Judkins technique. Coronary arterial narrowing of 70% or more in the luminal diameter was considered significant.

Biplane left ventriculograms in the 30° right anterior oblique and 60° left anterior oblique projections were recorded on 35-mm film taken at 50 frames/sec with a 9-inch image amplifier system (Angiorex/U-arm, Toshiba, Tokyo, Japan). Left ventricular wall motion was evaluated according to the reporting system of the American Heart Association on patients evaluated for coronary artery disease.

Treadmill Exercise Testing and Body Surface Mapping

Treadmill exercise test. Graded treadmill exercise tests were performed according to the Bruce protocol. All medication except a sublingual nitroglycerin tablet was stopped at least 24 hours before testing.

Map recording. Body surface mapping was performed with a body surface potential mapping system (model HPM-5100, Chunichi Denshi, Nagoya, Japan) before and 1.5 minutes after exercise. Eighty-seven electrodes were placed over the torso, 59 leads on the anterior chest, and 28 on the back. ECGs from these 87 unipolar leads with Wilson’s central terminal as reference, standard 12-lead ECGs, and the Frank X, Y, Z ECGs were sampled simultaneously. The stored signals of each ECG were then displayed on a graphic terminal (model 4006-1, Tektronix, Beaverton, Oregon). If noise was detected in any of the signals, data sampling was repeated. The flat portion of the PQ segment was chosen to be the baseline. After performing the baseline adjust-

Data analysis. The mapping data were processed off-line on a minicomputer (VAX 11/750, Digital Equipment, Maynard, Massachusetts) by means of the program for isochronal map analysis developed by our institution. For this analysis, the onset of QRS was determined from the superimposed Frank X, Y, Z leads and the spatial magnitude, and was called “zero time.” For each lead, the duration from zero time to the time of the most rapid decrease in QRS voltage (dV/dtmin) was determined and was designated “index of ventricular activation” (IVA) in this study. The body surface distributions of IVA were displayed in the form of a map and called the “IVA isochrone map” (IVA map). On the display of IVA maps, the rectangular area represented the torso surface, with the left half reflecting the anterior chest and the right half the back. Each contour line connected equal IVA points. The interval of isochrone lines was 5 msec.

In 40 normal volunteers, the mean (M) and standard deviation (SD) of 1) IVA before exercise, 2) IVA after exercise, 3) the difference between IVAs before and after exercise (ΔIVA), at each lead point, were calculated. To estimate the deviation of patient data from the normal value, the departure index (DI) at each lead was calculated as follows:

$$\text{DI} = (X - M)/SD, \text{where } X \text{ represents IVA at the corresponding lead of each patient. IVA departure maps before and after exercise, and the } \Delta \text{IVA departure map were constructed by illustrating lines of equal DI values. Contour lines were depicted at intervals of } 1 \text{ DI.}$$

Because we were interested in the prolongation of IVA, two or more neighboring lead points where the DI values were more than 2 on the IVA departure map were designated as the “+2SD area.”

Statistical Analysis

Statistical difference was examined by the Kolmogorov-Smirnov goodness of fit test, the unpaired $t$ test, or the $\chi^2$ test; a $p$ value less than 0.05 was considered significant.

Results

Normal Volunteers

IVA maps constructed from a mean value of 40 normal volunteers are illustrated in Figure 1. Figure 1 (Panel A) is a mean IVA map before exercise, and Figure 1 (Panel B) is a mean IVA map at 1.5 minutes after exercise. On these maps, IVA was shortest on the right upper back. Isochrone lines extended from the right upper anterior chest to the left anterior chest toward the left and down. After they reached the left lateral chest, isochrone lines propagated to
the back, toward the right. IVA was longest on the middle back. Normal volunteers had a consistency in the spatial distribution of IVA maps for each subject, both before and after exercise.

Whether IVAs in normal volunteers were normally distributed was examined by the Kolmogorov-Smirnov goodness of fit test. In several lead points, IVAs were not normally distributed (Figure 2). Those lead points were excluded from the later statistical procedures.

In only a few cases, were the distribution patterns of IVA maps slightly different from that of a mean IVA map in normal volunteers; isochrone lines were crowded on the right anterior chest and the right back. On these IVA departure maps, however, there were no +2SD areas.

Patients With Angina Pectoris

Of 48 patients studied, 28 had one-vessel disease, 12 had two-vessel disease, and eight had three-vessel disease. Of 28 patients with one-vessel disease, 12 had left anterior descending artery (LAD) disease, six had left circumflex artery (LCX) disease, and 10 had right coronary artery (RCA) disease. Of 12 patients with two-vessel disease, five had both LAD and RCA disease, five had LAD and LCX disease, and two had RCA and LCX disease.

Relation Between Index of Ventricular Activation Maps and Coronary Arteriographic Findings

Representative cases. Figure 3 represents IVA maps and IVA departure maps from a patient with LAD one-vessel disease. The left ventriculogram (LVG) of this patient showed no wall motion abnormality. On an IVA map before exercise (Figure 3, Panel A), the distribution pattern of IVAs was very similar to that in normal volunteers. On an IVA departure map before exercise (Figure 3, Panel C), there was no +2SD area. On an IVA map after exercise (Figure 3, Panel B), however, isochrone lines increased in density on the upper middle anterior chest as compared with normal volunteers, and IVAs at the lead points on the left anterior chest were longer than before exercise. On an IVA departure map after exercise (Figure 3, Panel D), the +2SD area was located on the left upper anterior chest. On a ΔIVA departure map (Figure 3, Panel E), the +2SD area was spread over the left anterior chest, reflecting increased IVAs after exercise in these areas.

Figure 4 represents IVA maps and IVA departure maps from a patient with RCA one-vessel disease. The LVG of this patient showed no wall motion abnormality. Before exercise (Figure 4, Panels A and C), the distribution pattern of IVAs was very similar to that in normal volunteers, and there were no +2SD areas. After exercise (Figure 4, Panel B), isochrone lines increased in density on the right lower chest as compared with normal volunteers, and IVAs at the lead points on the right lower chest were longer than those before exercise. There was, however, no +2SD area on an IVA departure map after exercise (Figure 4, Panel D). On a ΔIVA departure map (Figure 4, Panel E), however, +2SD area was spread over the lower thoracic surface, reflecting increased IVAs after exercise in these areas.

Patients with LCX one-vessel disease had various patterns in the spatial distribution of IVA maps and in the locations of +2SD areas on IVA departure maps.

Figure 5 represents IVA maps and IVA departure maps from a patient with two-vessel disease. This patient has combined LAD and RCA disease. The LVG of this patient showed hypokinesis in the anterolateral and apical segments. On an IVA map before exercise (Figure 5, Panel A), isochrone lines increased in density on the right lower chest, and an island-like zone of the delayed IVA was observed on the left anterior chest. On an IVA departure map before exercise (Figure 5, Panel C), the +2SD area was spread over the lower thoracic surface, the left anterior chest, and upper anterior chest, reflecting increased IVAs in these areas. After exercise (Figure
Before exercise, Panel A: IVA map before exercise. Panel B: IVA map after exercise. Panel C: IVA departure map before exercise. Panel D: IVA departure map after exercise. Panel E: ΔIVA departure map. On IVA departure maps, (+) indicates site of maximal departure index, (−) indicates site of minimum departure index, and dotted area indicates +2SD area. Maps are displayed as in Figure 1. Before exercise (Panels A and C), distribution pattern of IVAs was very similar to that in normal volunteers (Panel A) and no +2SD area was found (Panel C). But, after exercise (Panels B and D), isochrone lines increased in density on upper middle anterior chest as compared with those in normal volunteers, and IVAs on left anterior chest were longer than before exercise (Panel B), and +2SD area was found on left upper chest (Panel D). On ΔIVA departure map (Panel E), +2SD area was spread over left anterior chest.

5, Panels B and D), the distribution pattern of IVAs was very similar to that before exercise; and a +2SD area was found in the region similar to that before exercise. On a ΔIVA departure map (Figure 5, Panel E), a +2SD area was found in the small region on the left anterior chest and the left upper back.

Body Surface Distribution of Area With Abnormal Ventricular Activation Index

In one-vessel disease, patients with 90% or more coronary arterial narrowing tended to have greater numbers of lead points with +2 or greater DI
Before exercise (Panels A and C), isochrone lines increased in density on right lower chest, and island-like zone of delayed IVA was observed in left anterior chest (Panel A). +2SD area was spread over lower thoracic surface, left anterior, and upper anterior chest (Panel C). After exercise (Panels B and D), distribution pattern of IVAs was very similar to that before exercise (Panel B), and +2SD area was found in region similar to before exercise (Panel D). On ∆IVA departure map (Panel E), +2SD area was found in small region on left anterior chest and left upper back.

Patients with LAD disease had a +2SD area at the lead points mainly on the left anterior and later thoracic. On the other hand, patients with RCA disease had a +2SD area at the lead points mainly on the lower thoracic surface. Patients with LCX disease had a +2SD area at the lead points on the upper anterior chest and left lateral chest.

Consequently, we designated two areas corresponding to LAD and RCA disease to study whether the +2SD area can identify the obstructive coronary artery (Figure 7). These areas were defined according to the following: They had to have two or more neighboring lead points that had sensitivity (percentage of patients with LAD [or RCA] disease and +2 or greater DI) over 0% and specificity (percentage of patients without LAD [or RCA] disease and +2 or greater DI) over 90% for detection of LAD or RCA disease. Overlap lead points between LAD and RCA disease were excluded. On IVA departure maps (Figure 6), diagrams of body surface distributions of +2SD area in patients with one-vessel disease. Numerals in figure represent number of patients with +2SD area at each lead point on IVA departure maps before or after exercise, or on ∆IVA departure maps. Patients with left anterior descending artery (LAD) disease had +2SD area mainly at lead points on left anterior and lateral chest. Patients with right coronary artery (RCA) disease had +2SD area mainly at lead points on lower thoracic surface. Patients with left circumflex artery (LCX) disease had +2SD area at lead points on upper anterior chest and left lateral chest.
before or after exercise or ΔIVA departure maps, we defined positive for the presence of LAD (or RCA) disease when a +2SD area was observed in any lead of the area corresponding to LAD (or RCA) disease. Using this criterion, retrospective analysis of individual IVA departure maps of all patients revealed a positive predictive value for the presence of LAD disease of 77% and a negative predictive value of 50% (overall predictive accuracy, 63%). Retrospective analysis of all patients revealed a positive predictive value of 72% for the presence of RCA disease and a negative predictive value of 70% (overall predictive accuracy, 71%).

**Relation Between Index of Ventricular Activation Maps and Left Ventriculographic Findings**

Twenty-two patients showed hypokinesis on LVG. Fourteen of 22 patients with hypokinesis on LVG (64%) showed +2SD areas on IVA departure maps before exercise, whereas 11 of 26 patients without hypokinesis on LVG (42%) showed +2SD areas on IVA departure maps before exercise.

**Discussion**

The purpose of this study was to examine whether or not ischemic changes on electrocardiography could identify the site of myocardial ischemia and wall motion abnormality caused by myocardial ischemia. As a new index of ischemic change, we investigated local abnormalities on body surface isochrone maps in patients with angina pectoris.

**Previous Studies on Electrocardiographic Localization of Coronary Arterial Obstruction**

Previous studies have mainly investigated a correlation between the site of coronary arterial obstruction and the site of ST segment depression on exercise ECG.1-4,17,18 Mirvis,17 with an experimental analysis in dogs, concluded that the regional nature of myocardial ischemia was detectable in body surface distributions of ST segment but that the degree of spatial overlap might limit the value of such techniques in extending the usefulness of clinical exercise ECG. Clinically, Fox et al18 used 16-lead precordial mapping after exercise and postulated that the isolated disease of LAD, RCA, or LCX was present when ST segment changes were confined to the anterior, inferior, and lateral regions of the left hemithorax, respectively. In contrast, Dunn et al1 and Fuchs et al2 with the use of 12-lead ECG, Abouantoun et al3 with vectorcardiography, and Kubota et al4 with body surface mapping (87 lead-points) reported that the site of ST segment depression on exercise could not identify the anatomic site of coronary arterial obstruction. Figure 8 shows the body surface distributions of ST segment depression (±0.05 mV horizontal or downsloping) in each one-vessel disease in the present study. There was a lot of overlap in the site of ST segment depression among the three groups. This result indicated that the body surface distribution pattern of ST segment depression could not identify the anatomic site of coronary artery obstruction.

The lack of clear correlation can be caused by several factors. These include the presence or absence of collateral circulation, individual differences of coronary artery anatomy,19 heart position in relation to the electrode positions, or distance from heart to the electrodes.

**A New Approach in Detecting Coronary Artery Disease**

Because of the sensitivity and specificity limitations of exercise-induced ST segment depression, there has been a recent interest in the diagnostic value of the QRS complex response to exercise.

Increased R wave amplitude on the surface ECG at peak exercise has been observed frequently in patients with coronary artery disease.5,6 The physiological mechanism for these changes has recently been suggested to be intramyocardial conduction disturbance secondary to ischemia,9,20 change in contractility,21 or changes in heart rate and axis.22 The importance of changes in the R wave amplitude during exercise as a diagnostic index for coronary artery disease or ventricular function, however, was not agreed on.5-7

On the other hand, many investigators with an experimental analysis reported the changes in VAT during myocardial ischemia.8-10 Holland and Brooks8 reported that the QRS complex underwent a biphasic sequence with an initial small decrease in VAT indicating a transient increase in the conduction velocity of the ischemic tissue, and subsequently, a dramatic increase indicating a pronounced decrease in conduction velocity of the ischemic tissue. The
decrease in VAT during myocardial ischemia, however, was slight and brief. Ruffy et al.\textsuperscript{10} reported that the degree of regional myocardial ischemia was related quantitatively to the increase in QRS duration of subepicardial electrograms but not subendocardial electrograms. It was thought that the changes in intramyocardial conduction rather than in a specialized conduction system played the major role in determining VAT responses to acute myocardial ischemia.\textsuperscript{23,24} Muller et al.\textsuperscript{25} reported an increase of VAT in those leads overlaying the distribution of the occluded artery by epicardial mapping. Thus, there is a possibility that the site of coronary arterial obstruction is identifiable by investigating local abnormalities in ventricular activation sequences. It is clinically difficult to perform epicardial isochrone mapping; therefore, to evaluate ventricular activation sequences by means of body surface mapping, we measured the duration from the QRS onset to the time of the most rapid decrease in QRS voltage (IVA) and constructed IVA isochrone maps. We focused attention to the prolongation of IVA.

**Normal Volunteers**

Normal volunteers had a consistency in the spatial distribution of IVA maps for each subject and for both before and after exercise conditions. Isochrone lines propagated from the right upper anterior to left lateral chest and, finally, to the back. The leftward extension of the isochrone lines is thought to reflect the ventricular excitation from the septum to the left ventricular free wall.

To objectively estimate the deviation of patient data from the normal value, the departure map technique\textsuperscript{15,16} was adopted in the present study. In using this technique, however, it is significant whether IVAs in normal volunteers were normally distributed. The Kolmogorov-Smirnov goodness of fit test was used, and in several lead points, IVAs were not normally distributed. Those lead points were excluded from the later statistical procedures.

A few normal volunteers showed distribution patterns of IVA maps in which isochrone lines were crowded on the right anterior chest and the right back. On IVA departure maps, however, a +2SD area was not found. This suggests that our normal range is sufficiently reliable to detect local abnormalities on IVA maps in patients with angina pectoris.

**Patients With Angina Pectoris**

**Relation between index of ventricular activation departure maps and coronary arteriographic findings.**

We mainly investigated a correlation between the site of coronary arterial obstruction and the site of the +2SD area on IVA departure maps during exercise testing. Because, in this study, local abnormalities on IVA maps before exercise were considered partially influenced by myocardial ischemia, we included IVA departure maps before exercise in this study.

Whether the analysis of IVA maps provided information on the presence of coronary artery disease in a totally different test set was not studied because of the small number of patients. In one-vessel disease, however, patients with 90\% or more coronary arterial narrowing tended to have greater numbers of lead points with +2 or greater DI than patients with less than 90\% narrowing. These results suggest that the degree of the ischemia might be reflected on IVA maps.

Although there was a lot of overlap in distribution of +2SD areas among LAD, RCA, and LCX disease, our data revealed that there were differences in the distribution of +2SD areas between patients with LAD disease and patients with RCA disease. The +2SD area on the left anterior chest was considered specific to patients with LAD disease, and the +2SD area on the right lower thoracic surface was considered specific to patients with RCA disease. These distributions are not appreciated by conventional ECG methods. Concerning patients with LCX disease, further study is required because of their small population in this study.

Using our criteria (Figure 7), the predictive value of identifying any particular patient as having LAD or RCA disease was only moderately reliable. The change in IVA during the exercise test, however, was considered more discriminating than the change in ST segment. Thus, the results of this study demonstrate that the regional nature of the ischemia can be reflected in IVA maps.

Previous studies have investigated ventricular activation sequences by epicardial mapping; however, we constructed IVA isochrone maps from body surface unipolar ECGs. The potential on the epicardial surface is transmitted through the lungs, muscle layer, and skin to the body surface by fusion and smoothing of the potential. Accordingly, the body surface potential can be affected by the potential of the other part of epicardium to some extent, especially on the right chest and the back; this might be the limitation of the noninvasive tests. The greater part of the body surface potential at any point, however, is thought to be determined by the epicardial potential beneath it. Although IVA measured in this study can be somewhat different from the local activation time of the corresponding point of the epicardial surface, the results of this study indicated that body surface IVA isochrone maps reflected the normal left ventricular activation sequence and depicted abnormalities that corresponded well with the ischemic site in patients.

Thus, we believe that body surface IVA isochrone maps can be used clinically to determine the activation sequence in the heart.

**Relation Between Index of Ventricular Activation Departure Maps and Left Ventriculographic Findings**

The +2SD areas on IVA departure maps before exercise tended to be more frequent in patients with hypokinesis (64\%) than in patients without hypokinesis (42\%) but this difference was not significant. In general, local abnormalities in ventricular activation sequence were found in patients with myocardial
infarction, conduction disturbance, or left ventricular hypertrophy. Because these patients were excluded in this study, we thought that the influences of these factors could be eliminated. In this study, patients were significantly older than normal volunteers (p<0.01). Progressive, although variable, fibrosis of the intraventricular conduction system with advancing age has been reported; however, because recent studies have shown a lack of significant correlation between age and QRS duration, we thought IVA was not significantly influenced by aging alone.

Geer et al reported that, with a long-term reduction in blood flow, degeneration and necrosis of myofibers developed focally and repeatedly in the subendocardial myocardium in patients without evidence of acute or remote myocardial infarction. We suggested that these degenerations and necroses of myocardium might bring about wall motion abnormalities, and that local abnormalities in ventricular activation sequence might be caused by these degenerated tissues that prevented the propagation of excitation from the area that was activated early.

Limitations of Study

We tried to evaluate ventricular activation sequences by means of body surface mapping in this study. Designation of IVA on body surface unipolar ECGs has not been solved theoretically or experimentally. In this study, the minimum dV/dt point was chosen as the point for the estimation of IVA. It was thought that the minimum dV/dt point was superior to the peak R point for detection of abnormal IVA prolongation because the standard deviation in the minimum dV/dt of normal volunteers was less than in the peak R time, and therefore, the minimum dV/dt point was thought to be relatively stable during various states (i.e., respiration, position, or exercise).

In several lead points, IVAs in normal volunteers were not normally distributed. Those lead points, however, might be decreased by increasing the numbers of normal volunteers and classifying them according to constitution, sex, or age.

In this study, normal volunteers were all men. Goldberger and Bhargava reported that QRS duration in men, assessed by high-frequency filtration in orthogonal leads, was greater than in women, and this difference was probably, in part, a function of difference in cardiac mass. Therefore, there might be sex-related IVA differences; and if so, local abnormalities in ventricular activation sequence might be underestimated in female patients by the departure map technique. Further study must be conducted to address this problem.

Conclusion

The present study demonstrated a close relation between local abnormalities on IVA maps during the exercise test and the findings of coronary arteriography. These results indicate that IVA maps have more useful information than conventional analyses of ECGs for detecting the site of myocardial ischemia in patients with angina pectoris. Although the results of this study are preliminary, IVA maps represent a potential new index of myocardial ischemia.

References

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KEY WORDS • isocron map • departure map • body surface electrocardiographic mapping • myocardial ischemia • coronary artery disease
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