Quantitative assessment of myocardial ischemia and necrosis by continuous vectorcardiography and measurement of creatine kinase release in patients

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ABSTRACT The accuracy of the use of the maximal QRS vector difference to estimate myocardial infarct size irrespective of infarct location was compared with that of measurement of cumulative creatine kinase (CK) release. Sixty patients with acute myocardial infarction and a history of symptoms of less than 4 hr duration were followed for 24 to 72 hr with orthogonal vectorcardiography and CK release analysis. Spatial QRS vector differences were calculated between the first QRS complex recorded and subsequent QRS complexes at timed intervals. The QRS vector difference increased rapidly and reached a plateau at an average 12.1 hr after onset of symptoms, as compared with 34.0 hr for the cumulated CK release. In 42% of the patients a stepwise progression of infarct evolution was observed. Irrespective of infarct location the maximal spatial ST vector magnitude was related to the ultimate QRS vector difference (r = .80) and to the cumulative amount of CK released (r = .64). Furthermore, maximal QRS vector difference correlated well with the maximal cumulative CK release (r = .64) Ten patients had possible infarct expansion, as indicated by recurrent QRS changes without concomitant CK release. Fifteen patients had infarct extension that was indicated by secondary CK release and that in seven patients was associated with further QRS changes. Infarct extension caused an approximate 25% increase in infarct size. Spatial ST vector magnitude, QRS vector difference, and cumulative CK release are complementary measures in the quantification of evolving myocardial injury after acute coronary occlusion and in the determination of sequels to therapeutic interventions.

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ACUTE MYOCARDIAL ISCHEMIA and infarction are dynamic processes and information on the size and progression of infarction with time is potentially important in coronary care. The use of continuous vectorcardiography (VCG) to monitor patients was suggested by Hodges et al.,¹ and has been further adapted for the evaluation of acute myocardial infarction (AMI).²⁻⁵ Serial analysis of spatial VCGs permits a simple and convenient determination of temporal and quantitative changes in the QRS complex and ST segment. In contrast to precordial electrocardiographic mapping, which applies quantitatively only to anterior myocardial infarcts, spatial VCG can be used irrespective of infarct location since the electromotive forces are reduced to three equipotential orthogonal leads.

ST segment deviations vary markedly during the early phase of an AMI and continuous recording is necessary to capture the maximum deviation. In animal experiments this value defines the area of the reversible injury and predicts the ultimate infarct size.⁶⁻⁷ QRS changes closely reflect myocardial cell death⁸ and serial analysis of VCGs may provide important information about the rate and extent of infarction. The vectorial deviations of the QRS complex from preinfarction values theoretically reflect the loss of electrically active myocardium due to irreversible damage.⁹⁻¹⁰ This vector difference has been shown to correlate with morphometric measurements of infarct size in animal experiments.¹¹⁻¹² In the clinical setting the premorbid reference VCG is rarely available. However, the onset of symptoms does not necessarily mean that the necrotic process has started but simply that the patient has ongoing myocardial ischemia. Necrosis, as reflected by changes in the QRS complex, may develop after various time intervals, but usually begins developing after 1 to 2 hr.¹³ Thus, when obtained early, the first QRS complex may prove valid as a reference value.

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DIAGNOSTIC METHODS—MYOCARDIAL INFARCTION

In this study we have examined the possible usefulness of continuous recordings of spatial ST and QRS vectors in the assessment of the evolution of ischemia and necrosis in AMI and compared these indices with the cumulative release of myocardial creatine kinase (CK).

Patients and methods

Sixty patients (45 men and 15 women, age range 37 to 78 years) with AMI completed this study. All patients fulfilled the following inclusion criteria: (1) no previous history or past electrocardiographic sign of myocardial infarction, (2) admitted within 4 hr after onset of symptoms, (3) no intraventricular conduction defects (QRS duration ≤ 0.11 sec), (4) typical symptoms for more than 30 min and ST segment elevation > 1 mm in leads I, II, III, aVL, and aVF or > 2 mm in V5 through V6, (5) no pericardial friction rub on admission. None of the patients received intramuscular injections or required cardiovascular during the study period, and no patients showed severe electrolyte disturbances. Twelve patients were excluded from the study, five because they did not survive long enough for adequate CK and VCG analysis and seven because they developed bundle branch block or QRS duration > 0.11 sec.

Blood samples for CK analysis were drawn every second hour until the twelfth hour and thereafter every fourth through sixth hour up to 72 hr. The enzyme concentration was measured by a standard Autoanalyzer technique.14 Accumulated CK release was computed from the time-activity curves assuming a first-order elimination from one compartment. If the descending limb of the time-activity curve was smoothly declining over at least five consecutive observations, an individual elimination rate constant, kdp, was calculated by exponential curve fitting of these segments. Otherwise a standard kdp of 0.0576 hr-1, equivalent to the mean value of all individual kdp’s, was used for calculating the cumulative CK release curves. This procedure was chosen to avoid spuriously low kdp’s due to recurrent or continuous CK release. A polyphasic CK release was defined as two or more distinct plateaus in the cumulative CK curve, each differing more than 10% from the previous one. CK plateau levels (CKmax) and the corresponding time from onset of symptoms to plateau level (CK release time) were determined from each curve.

As soon as possible after admission, electrodes were attached to the patients according to the Frank orthogonal lead system.15 The X, Y, and Z lead tracings were continuously recorded for 24 hr with an ICR vectorcardiograph connected to an analog tape recorder running at 15/16 inch/sec (2.38 cm/sec). Sequential analysis of the ST and QRS vectors were done hourly and plotted as a function of time.

The spatial ST vector magnitude (ST-VM) was calculated with the formula

\[ \text{ST-VM (mV)} = \sqrt{X^2 + Y^2 + Z^2} \]

where X, Y, and Z represents the coordinates of the ST projections on the three orthogonal axes: X, right to left; Y, head to foot; and Z, anterior to posterior. ST-VM was calculated 20 msec after the termination of the QRS complex (J point) and the isoelectric baseline was drawn between adjacent PQ segments.

All scalar QRS complexes were digitized on a microcomputer system. The horizontal resolution corresponded to 2 msec and the vertical resolution to 2.5 μV. The onset and offset of the QRS complex was visually determined. For each lead the QRS complex was summed between onset and offset. These sums represent the Cartesian coordinates of the summation vector for each beat. The reproducibility of this procedure was tested and gave a coefficient of variation of 4% for repeated measurements. The first recording obtained was chosen as the reference and all subsequent recordings were vectorially subtracted from this to give the QRS vector difference (QRS-VD) according to the formula

\[ \text{QRS-VD (μV·sec)} = \sqrt{(\Sigma X_r - \Sigma X_s)^2 + (\Sigma Y_r - \Sigma Y_s)^2 + (\Sigma Z_r - \Sigma Z_s)^2} \]

where \( \Sigma X, \Sigma Y, \) and \( \Sigma Z \) denote lead sums from onset to offset of QRS complex, \( r \) is the reference beat, and \( i \) is the current beat.

The QRS-VD and ST-VM were plotted as a function of time from onset of symptoms. From these graphs the following parameters were determined: maximal ST-VM recorded during the registration period (ST-VMmax), maximal QRS-VD (QRS-VDmax), and the duration of the QRS vector evolution from onset of symptoms to plateau level (QRS evolution time). Polyphasic evolution of the QRS vector changes was arbitrarily defined as a new permanent change of at least 10%, preceded by a plateau of more than 2 hr duration.

Statistical computations were performed with the BMDP-81 package (Biomedical Computer Programs, Health Sciences Computing Facility, UCLA). Comparison of group means was with Wilcoxon nonparametric statistical analysis. All values are given as mean and range.

Results

The sampling of CK and recording of VCGs began on average 2.55 (0 to 4.0) hr after onset of symptoms.

Monophasic infarct evolution. Monophasic infarct evolution as reflected by the cumulative CK release and the QRS-VD was found in 35 of the 60 patients. Figure 1, A, illustrates a typical monophasic infarct evolution. Average CKmax for the monophasic infarcts was 3197 (110 to 7900) IU/1 and QRS-VDmax was 25.0 (2.6 to 68.9) μV·sec. The average CK release time was 27.4 (8.0 to 50.0) hr and was considerably longer than the QRS evolution time of 9.7 (1.0 to 19.0) hr (p < .001).

The relationship between CKmax and QRS-VDmax is shown in figure 2, and suggests an association between the two independent indices of myocardial necrosis (r = .65). The average ST-VMmax for monophasic infarcts was 0.264 (0.050 to 0.590) mV and was reduced by 27% after 1 hr (p < .001). A close correlation was obtained between ST-VMmax and QRS-VDmax (r = .80; figure 3, closed circles) and between ST-VMmax and CKmax (r = .69; figure 4, closed circles). Separate examination of 13 patients admitted within 2 hr of onset of symptoms showed no significant differences in the regressions between ST-VMmax and QRS-VDmax, ST-VMmax and CKmax, and QRS-VDmax and CKmax, but the dispersions were smaller for the early admissions.

Biphasic infarct evolution. Biphasic infarct evolution was found in 25 patients (42%); in 15 patients it was evident from the CK release curves and in 17 patients it

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was evident from the QRS-VD curves. In only seven of these patients was a biphasic course observed for both parameters. Figure 1, B, illustrates a biphasic infarct evolution pattern. Details on CK release and QRS-VD evolution for monophasic and biphasic infarcts are given in Table 1.

CK release time and QRS evolution time to the first plateau of biphasic infarcts (phase I) were similar to times to first plateau of monophasic infarcts. The time to the second plateau of biphasic infarcts (phase II) was about 80% longer than that to the plateau of monophasic infarcts (p < .001) and to phase I of biphasic infarcts (p < .001). The magnitudes of CKmax and QRS-VDmax both increased by 25% from phase I to phase II. Neither of these measures were statistically different from CKmax and QRS-VDmax of monophasic infarcts. Phase II was normally preceded by a recurrent rise in ST-VM. To define the importance of ST-VMmax as a determinant of ultimate infarct size in biphasic infarcts, regressions of ST-VMmax vs QRS-VDmax and CKmax were performed for phase I and phase II. The best relationships were obtained for phase II and they conformed to the corresponding monophasic regressions (Figures 3 and 4, open circles; r = .81 and .59 for ST-VMmax vs QRS-VDmax and CKmax, respectively). The relationship between CKmax and QRS-VDmax for phase II closely matched that for monophasic infarcts (Figure 2, open circles; r = .62) and the combined regression was CKmax = 75.5 × QRS-VDmax + 1330 (r = .64). In further analysis terminal values for CK release and QRS-VD were used irrespective of monophasic or biphasic infarct course.

**Infarct location.** There were 28 anterior and 32 inferior infarcts. Salient data are listed in Table 2. Inferior infarcts tended to have somewhat longer CK release and QRS evolution times and to be smaller, as reflected by the CK release, the QRS-VD evolution, and ST-segment changes, when compared with anterior infarcts. However, only the difference in QRS-VDmax values reached significance (p = .034). Infarct location did not influence the relationship between ST-VMmax and QRS-VDmax, ST-VMmax and CKmax, or between QRS-VDmax and CKmax. Seven patients had left anterior hemiblock and two patients had left posterior hemiblock. The relationships between ST-VMmax and QRS-VDmax and between QRS-VDmax and CKmax ob-

**FIGURE 2.** The relationship between the ultimate CKmax and QRS-VDmax (n = 51). The r value given is for all patients. For monophasic infarcts alone r = .65 and for biphasic infarcts r = .62. The regression equation for all patients is CKmax = 75.5 × QRS-VDmax + 1330.
Discussion

Assessment of myocardial necrosis by measurement of cumulated CK release is an empirical method that has been well documented in experimental animals and patients and correlations of .75 to .93 have been found between cumulated CK release and morphometrically measured infarct size in man. The method has several limitations, however.

Myocardial enzyme release reflects cell membrane permeability changes rather than the occurrence of cell death and will not correctly define the temporal progression of infarction. Furthermore, the appearance of enzymes in circulating blood is delayed by the lag phase between the different enzyme compartments.

The fraction of CK retrieved from the blood volume is probably about 20% of the total myocardial CK depletion. Impaired washout of CK from areas with severely reduced blood flow leading to prolonged exposure to the myocardial lymph with subsequent inactivation may further reduce this fraction in patients with large infarcts. Accordingly, large infarcts may be underestimated by CK analysis.

Incorrect estimates of $k_0$ due to continuing CK release, fluctuations in blood volume, and drug effects may impair estimates of infarct size. The mean value and range of $k_0$ observed in this study was comparable to that obtained in a previous study and was unrelated to the infarct size reflected by CK release and the independent QRS-VD. Furthermore, $k_0$ was unrelated to infarct duration and infarct location.

Electrocardiographic changes have been used as complements to enzyme analysis to describe acute ischemic injury and ultimate myocardial necrosis. The use of precordial ST-QRS mapping, as described by Maroko et al., is restricted to estimation of anterior infarcts. In contrast, VCG can be used irrespective of infarct location and a spatial vector can be constructed assuming that the electrical activity of the heart can be represented by dipoles and that the orthogonal leads are equipotential. These assumptions have been criticized.

Regional intramyocardial conduction delays may occur with myocardial infarction. If true vectorial summation of the different regional dipoles can be performed, conduction delays should not interfere with the electrical activity of the heart.

FIGURE 3. The relationship between the initial spatial ST-VM and the final maximal QRS-VD (n = 56). The r value given is for all patients. For monophasic infarcts alone r = .80 and for biphasic infarcts r = .81. The regression equation for all patients is QRS-VD_max = 72.8 x ST-VM_max + 7.0.

Elimination rate of CK. Individual $k_0$ was calculated in 44 patients and averaged 0.0576 (0.0276 to 0.0810) hr$^{-1}$. Correlation analysis suggested that $k_0$ was not related to CK max, QRS-VD max, or QRS evolution time.

FIGURE 4. The relationship between the initial spatial ST-VM and the final cumulative CK release (n = 58). The r value indicated is for all patients. For monophasic infarcts alone r = .69 and for biphasic infarcts r = .59. The regression equation for all patients is $CK_{max} = 7180 \times ST-VM_{max} + 1530$. 

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TABLE 1
VCG and cumulative CK changes in monophasic and biphasic infarcts

<table>
<thead>
<tr>
<th></th>
<th>Monophasic infarcts (n = 35)</th>
<th>Biphasic infarcts (n = 25)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>First phase</td>
</tr>
<tr>
<td>ST-VMmax (mV)</td>
<td>0.264 (0.050–0.590)</td>
<td>0.276 (0.010–0.760)</td>
</tr>
<tr>
<td>QRS-VDmax (µV·sec)</td>
<td>25.5 (2.6–68.9)</td>
<td>21.1 (9.5–39.2)</td>
</tr>
<tr>
<td>CKmax (IU/l)</td>
<td>3197 (110–7900)</td>
<td>3103 (190–7100)</td>
</tr>
<tr>
<td>QRS evolution time (hr)</td>
<td>9.7 (1.0–19.0)</td>
<td>9.2 (3.0–15.0)</td>
</tr>
<tr>
<td>CK release time (hr)</td>
<td>27.4 (8.0–50.0)</td>
<td>27.4 (9.0–39.5)</td>
</tr>
</tbody>
</table>

ST-VM at start of recording. Plateau values of QRS-VD and cumulative CK release are given for monophasic and for the first and second levels of biphasic infarcts. QRS evolution and CK release times from onset of pain to each plateau are given. All values are expressed as mean and range.

with the QRS integrals since these are computed over the entire QRS complex, thereby eliminating effects of altered activation sequence. However, the present study was not designed to evaluate effects of major changes in ventricular conduction and patients developing bundle branch blocks were excluded. The relationships between QRS-VDmax, ST-VMmax, and CKmax observed in patients presenting with left ventricular hemiblocks conformed to those observed overall. During AMI early R wave changes unrelated to tissue necrosis may cause erroneous estimates of infarct evolution.28 The changes have been attributed to reduced conductivity, displacement of the isoelectric baseline, or increased volume of the ventricles.29 They were, however, of a very transient nature and subsided within 1 to 2 hr of onset of symptoms.30

Despite these objections, good correlations between VCG estimates and postmortem examinations of infarct size in baboons31 and dogs32, 33 have been shown. A close relationship between morphometric infarct size and the integral of initial spatial vector magnitude (r = .90) in patients has recently been reported32 and a QRS score derived from the standard 12-lead electrocardiogram has been shown to relate to morphometric assessments of anterior (r = .80)33 and inferior infarcts (r = .74).34 Although the QRS-VD and cumulated CK release are indirect measures of infarct size, the correlation between these indices obtained in the present study conforms well to results reported previously17-19, 32-34 and suggests that the QRS-VDs provide an estimate of infarct size. This result is in contrast to that of Wikswo et al.,35 who found no relationship between CK release and QRS changes. The discrepancy may be explained by the small number of subjects in their study and their inclusion of patients with previous myocardial infarction or a history of symptoms of up to 6 hr. The use of a constant kD for calculating cumulated CK release may also have adversely affected the relationship between CK release and QRS changes. Studies with precordial mapping support an association between CK release and QRS changes in anterior infarcts.36-38 The present study extends these findings to inferior infarcts.

One problem associated with infarct sizing from QRS changes is the lack of a preinfarction reference. In dog experiments Hillis et al.13 found that the size of the Q wave at 2 hr after occlusion was about a seventh of the final Q wave at 24 hr. However, myocardial infarction evolves more rapidly in dogs than in humans. Separate examination of the patients admitted within or after 2 hr of onset of symptoms did not show any significant differences in the regression of QRS-

TABLE 2
VCG and cumulative CK changes with respect to infarct location

<table>
<thead>
<tr>
<th></th>
<th>Anterior infarcts (n = 28)</th>
<th>Inferior infarcts (n = 32)</th>
<th>Total n = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-VMmax (mV)</td>
<td>0.318 (0.050–0.640)</td>
<td>0.232 (0.010–0.760)</td>
<td>0.269 (0.010–0.760)</td>
</tr>
<tr>
<td>QRS-VDmax (µV·sec)</td>
<td>32.3 (8.8–68.9)</td>
<td>21.0 (5.7–49.6)</td>
<td>25.7 (5.7–68.9)</td>
</tr>
<tr>
<td>CKmax (IU/l)</td>
<td>3851 (110–8100)</td>
<td>3052 (380–6200)</td>
<td>3410 (110–8100)</td>
</tr>
<tr>
<td>QRS evolution time (hr)</td>
<td>11.0 (1.0–23.0)</td>
<td>13.3 (3.0–30.0)</td>
<td>12.1 (1.0–30.0)</td>
</tr>
<tr>
<td>CK release time (hr)</td>
<td>30.7 (8.0–55.0)</td>
<td>37.2 (13.0–70.0)</td>
<td>34.0 (8.0–70.0)</td>
</tr>
</tbody>
</table>

ST-VM at start of recording. Ultimate values for QRS-VD and cumulative CK release are given. QRS evolution and CK release times are relative to onset of symptoms.
VD_{max} vs CK_{max}, although the correlation coefficients were higher for those admitted early. These results indicate that a VCG obtained within 4 hr of onset of symptoms may be a valid reference for infarct size estimation.

The use of ST segment changes as an indicator of ischemia and predictor of ultimate myocardial necrosis has been well established, despite theoretical limitations.^{39} ST segment changes are maximal within minutes after onset of myocardial ischemia and are subsequently reduced as infarction evolves or the ischemia is reversed. This implies that the true ST-VM_{max} may be underestimated in many patients. The reduction in ST-VM of 27% after 1 hr emphasizes the importance of early and continuous recording in obtaining the ST-VM_{max} that, indirectly, is the tissue at risk of necrosis. In the present study the ST-VM_{max} related equally well to the ultimate QRS-VD and cumulated CK release. Recordings obtained later than 4 hr after onset of pain are probably less representative of the ST-VM_{max} and therefore are not very useful as a predictor of the final QRS vector changes.

About 40% of the patients showed electrocardiographic or enzymatic evidence of biphasic infarct evolution. Different pathophysiologic mechanisms may be reflected by the stepwise changes in the respective curves. Short-term changes in left ventricular volume or thinning of the infarcted area without extension of the actual necrosis have been shown to produce change in the QRS complex.^{40,41} In the present study, 10 patients (17%) had a second permanent change in the QRS-VD that was not accompanied by further CK release, and this presumably reflected infarct expansion. Seven patients (12%) demonstrated a recurrent rise in QRS-VD and cumulative CK release that strongly suggested infarct extension. In eight patients (13%) secondary CK release was observed without associated QRS changes. This may be explained by insufficient VCG observation time or increase in plasma CK independent of infarct extension caused by changes in plasma volume or increased washout of extravascular CK. Thus, between 12% and 25% of the patients in this study showed infarct extension. This is close to the incidence reported in previous studies.^{30,40,42}

The observation that ST-VM_{max} correlated better with QRS-VD_{max} and CK_{max} of the second plateau than of the first plateau indicates that the ultimate size of the necrosis is defined by the ischemia early after coronary occlusion. However, part of the jeopardized myocardium will not be irreversibly injured until much later, as indicated by the QRS evolution time of 9.2 hr to the first plateau vs 17.6 hr to the second plateau. This may be due to nonuniform residual flow that results in different capacity for survival. This has considerable bearing on the use of early intervention to limit infarct size.

Patients with anterior wall infarcts tended to have a higher ST-VM_{max}, QRS-VD_{max}, and CK_{max} than inferior infarcts. This is probably due to the fact that in humans a larger myocardial mass is supplied by the left anterior descending artery than by the right circumflex artery. The QRS evolution time was not related to infarct size, but the time to complete the infarction was shorter in anterior than in inferior infarcts (table 2), confirming the results of a previous study.^{2}

No single index presently available can accurately assess the progression of the ischemic injury and the ultimate infarct size. The changes in the VCG and the enzyme release therefore have to be used as complementary indices. The present study shows that these indices may be particularly valuable in trials of treatment aimed at limiting infarct size. Continuous analysis of the VCG permits semiquantitative assessment of the evolving myocardial ischemia and infarction. Because infarct size varies over a wide range a large patient group is needed to detect infarct reduction. The group size can be reduced if the method of comparing the infarct size predicted from initial ST-VM with the observed size as measured by CK release and QRS-VD is used. From this study it may be calculated that to detect a 30% reduction of infarct size predicted from the ST-VM_{max} obtained early, a minimum of 60 patients per group will be required to show a statistical difference at $\alpha = .05$ and 1-\beta (power) = .80.

Since the QRS-VD on average evolves in less than 10 hr early intervention has to be started within 4 to 6 hr after onset of symptoms in order to prove effective.

References


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