Detection and localization of coronary artery disease with body surface mapping in patients with normal electrocardiograms

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ABSTRACT Patients with clinically significant coronary artery disease often have normal resting electrocardiograms. Clinical and experimental studies have shown that body surface potential maps provide improved recognition of some disease states and more regionally selective information than standard electrocardiograms. Body surface maps were recorded at rest from 41 symptomatic patients with angiographically documented coronary artery disease and normal electrocardiograms. Patient maps were statistically compared with maps recorded from 644 normal subjects with the use of previously reported data representation technique. By this technique, maps from patients with symptomatic coronary artery disease and normal electrocardiograms were separated from maps of normal subjects with a sensitivity and specificity greater than 94%. The majority of discriminating information was present in the QRS interval. Fifteen of the 41 symptomatic patients had documented single-vessel coronary disease and their maps were separately compared with normal maps. Average maps from each of three patient groups with single-vessel disease contained abnormal patterns during the QRS interval that were unique to the vessel affected. In comparison with an average map from normal subjects, the average map from the group with left anterior descending coronary disease showed lower potentials over the anterior and inferolateral thorax during the early to mid QRS interval, the average map from the circumflex disease group showed decreased potentials around the entire inferior thorax in the mid to late QRS interval, and the average map from the right coronary disease group showed decreased potentials over the right anterior thorax during the mid to late QRS interval. Multivariate statistical analysis of body surface maps detected resting, regional electrophysiologic abnormalities associated with coronary artery disease and maps may have utility in diagnosis of coronary artery disease in patients with normal electrocardiograms.


PATIENTS with clinically significant coronary artery disease often have a normal resting electrocardiogram. Previous studies have shown 25% to 50% of patients with a history of chest pain due to documented coronary artery disease have normal resting electrocardiograms when they are pain free.1–3 These studies included patients with both single and multivessel disease. Other studies have shown that in patients with coronary artery disease and no history of infarction, the most common electrocardiographic abnormalities are nonspecific and occur during the ST-T interval.4

Compared with the 12-lead electrocardiogram, body surface potential mapping provides enhanced sensitivity to individual cardiac regions and improved electrocardiologic recognition of some disease states.5–8 Previous studies have shown that patients with coronary artery disease and normal electrocardiograms can be discriminated from normal subjects with the use of body surface potential maps.9–11 These studies relied primarily on analysis of the ST-T interval, a portion of the electrocardiogram affected by a variety of nonpathologic factors.

The study reported here was undertaken to determine whether the added information content of resting body surface potential maps of the entire QRST interval could be used to detect the presence and location of documented coronary artery disease in symptomatic patients with normal resting electrocardiograms.

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Methods

Coronary disease patients. Body surface maps were recorded from 37 men and four women referred for coronary angiography because of chest pain. Age range of the study patients was 41 to 74 years (mean 58). Body surface maps, electrocardiograms, and coronary angiograms were all obtained during the same hospitalization. Maps and electrocardiograms were recorded with the patient resting and pain free. Three patients had a history of prior documented myocardial infarction without QRS abnormalities. Infarction was confirmed by history of typical chest pain, changing ST-T wave abnormalities, and positive isoenzyme tests. These three patients were studied more than 1 year from the date of myocardial infarction. None of the study patients had clinical evidence of congestive heart failure or valvular heart disease. All patients gave informed consent for body surface mapping and the study protocol had the prior approval of the Institutional Review Board of the University of Utah.

Electrocardiograms of all study patients were independently read as normal by two cardiologists. The first reader, the member of the cardiology staff reading tracings the day of the patient’s admission, was unaware of inclusion of the tracing in this study. The second reader was a part of the study team (L. S. G. or C. W. H.). Patients were not included unless there was agreement on interpretation. PR, QRS, and QT intervals were within the normal range on all electrocardiograms. Only patients undergoing cardiac catheterization and coronary angiography for clinical indications were considered for the study. Patients were included in angiograms showed luminal diameter stenosis of 50% or greater of one or more of the three main coronary arteries or left main coronary artery. Fifteen patients had isolated single-vessel coronary disease. Of these, eight patients had left anterior descending stenosis, four had circumflex stenosis, and three had right coronary stenosis. Of the remaining 26 patients, 14 had two-vessel coronary disease and 12 had three-vessel coronary disease. One patient in the two-vessel disease group and one in the three-vessel disease group also had left main coronary artery stenosis of 50% or greater. None of the 41 patients had hypertension at the time of catheterization, none were taking antiarrhythmic drugs, and all were in sinus rhythm with normal electrolytes.

Clinical characteristics of the patients with coronary artery disease are shown in Table 1. None of the patients had evidence of akinesis or dyskinesia during left ventriculography and 28 patients (68%) had normal ventriculograms. Thirteen patients had hypokinesis of a ventricular wall segment in the regions listed. These findings are in agreement with previously published studies indicating that severe wall motion abnormalities are rare in patients with coronary artery disease and normal 12-lead electrocardiograms. Treadmill exercise tests were positive in 20 patients, negative in seven, and 14 did not undergo exercise testing.

Normal subjects. Body surface maps from 419 normal men and 225 normal women between the ages of 30 and 72 years (mean age 41 years) were used for comparison with the maps from patients with coronary artery disease. These normal maps were the data base for a previous report from our laboratory. None of the normal subjects had undergone catheterization.

Recording techniques. All maps were recorded with the use of a 32-lead body surface mapping system developed in our laboratory. Characteristics of this system have been reported. The maps were displayed and analyzed as 192 lead maps estimated from 32-lead recordings. A Wilson central terminal served as the reference electrode. All 32 leads were sampled at 1000 Hz with the use of multiplexer recording techniques and digitized data were stored on floppy disks for processing.

Map processing. An interactive computer program was used to baseline and gain adjust all electrocardiographic signals. The TP segment was used as the baseline. A QRS complex from one lead was used as a template that was cross correlated with five to 15 additional QRS complexes. The cross correlation peaks were used as fiducial markers to time align the complexes that were then averaged. Averaging was used to increase the signal-to-noise ratio. Map frames were analyzed at 1 msec intervals but were displayed at 5 msec intervals during the QRS and 20 msec intervals during the ST-T. All maps were displayed treating the thorax as a cylinder unrolled from the right axillary line. The top of each map was the level of the manubrium and the bottom the level of the umbilicus. The front and back of the thorax were marked. A vertical line on a reference electrocardiogram was displayed above each map to indicate the time of the map frame during the QRST interval. Contour lines of maps were displayed at 0.1 mV increments during QRS interval and 0.05 mV increments during the ST-T interval. All maps were individually checked for signal quality. Sites at which signals were noisy or absent were estimated from all other sites with least mean square estimation.

Map classification. All body surface maps in this study were analyzed by a previously reported spatial and temporal data representation technique. This technique reduces data redundancy and allows representation of each patient map by 216 independent coefficients unique to that map. The method is similar to the statistical technique of canonical representation of dependent variables. These 216 coefficients along with 18 temporal and 12 spatial bases can be used to reconstruct the potential at any lead at any time in the QT interval to an average error of 64 μV root-mean-square (rms) for the QRS interval and 23 μV rms for the ST-T interval. The method permits reconstruction of low-level and complex map features. Since each of the 216 coefficients from a single map is an independent variable, conventional statistics can be used to quantitatively discriminate map features between pairs of clinically classified subject groups.

Computer classification of maps was based on feature extraction to select a small subset of the 216 representation coefficients and a nonlinear classifier that used estimates of the subset mean vectors and covariance matrices of each group (coronary disease and normal). Since the representation coefficients were inde-
pended, the t test was used to select the subset of coefficients that were ordered by magnitude of the t statistic. The number of coefficients used in the classifier was less than 3% of the sum of the number of map subjects in the entire comparison and less than 50% of the smallest number of subjects in any class, in this case, the 41 patients with coronary artery disease. Mean vectors and covariance matrices of the selected coefficients were calculated for each class. By the use of jackknifing (the leave-one-out method), each patient was classified with a Mahalanobis metric that is a nonlinear discriminant function parametric in feature mean vector and covariance matrix. Details and other examples of this classification procedure have been published.12, 15 Sensitivity and specificity were determined from the number of correct, false-positive, and false-negative classifications. Since classification criteria are derived from complex mathematical operations on canonical variables that have no explicit physiologic meaning, they are not included as part of the results. However, for any dichotomy tested, the procedures used to produce a discriminant value along with the threshold can easily be implemented on virtually any computer, making the classification procedure applicable clinically.

Comparison of average maps from clinical groups. To visually identify map features differing between the patients with coronary artery disease and normal subjects, a special type of map termed a feature difference map was computed.12 Since each map was represented by 216 independent coefficients, averages and variances were calculated for each of the 216 coefficients to represent an average map for the coronary artery disease group and for the normal group. Values of the 20 coefficients from the average map for patients with coronary disease that were significantly different at the p<.01 level were identified by Student’s t test. A feature difference map was next computed from the 20 coefficient differences by subtracting the appropriate coefficients of the average normal map from the coefficients of the average map for the coronary disease group. The feature difference map was displayed as a sequence of potential distributions of only the significant maps features differing between average maps of the two clinically defined groups. This map display enhanced discrimination between map features since insignificant feature differences were not displayed.

Average maps from each of the three single-vessel coronary disease groups were compared with an average normal map in a nonstatistical way. An average map for each single-vessel disease group was calculated again by averaging the 216 coefficients representing each map in each clinical class of single-vessel coronary disease. The average normal map was then subtracted from the average map for each single-vessel disease group with the use of all 216 coefficients. This type of difference map displayed all differences between average maps for each clinical class whether significant or not. Statistically based feature difference maps comparing average maps for each single-vessel disease group and that for normal subjects were not calculated because the small number of patients made this type of computation meaningless.

Calculation of average maps required time normalization of individual maps. Time normalization assumes that similar physiologic events are occurring at similar times in all maps being compared. While not a proof that this assumption is correct, QRS duration was measured in all individual maps to see whether significant differences existed between the patients with coronary disease and normal subjects. QRS duration was manually determined from the display of rms voltage across all leads vs time. The mean QRS duration for the 41 patients with coronary artery disease was 91.8 ± 10.9 msec and that for the 644 normal subjects was 92.1 ± 10.8 msec. The difference between these two measurements was not statistically significant.

Results

Table 2 lists the classification matrix resulting from a statistical comparison between maps for normal subjects and the maps for patients with coronary disease with the use of the 216 spatial and temporal data representation coefficients previously described. The 20 most significantly different features, 12 from the QRS interval and eight from the ST-T interval were used. One of 41 maps from the coronary artery disease group was incorrectly classified as normal and 40 of 644 maps from normal subjects were incorrectly classified. There was therefore one false-negative and 40 false-positive results, for a sensitivity of 98%, a specificity of 94%, and an overall accuracy of 94%. The one patient with coronary artery disease whose map was misclassified as normal had disease involving the left anterior descending and right coronary arteries and no history of infarction. The group of those receiving false-positive classifications included 16 women and 24 men, a male-to-female ratio similar to that in the total normal group. Since none of the normal subjects had undergone cardiac catheterization, it is possible that some may have had asymptomatic coronary disease.

Maps of individual patients with coronary artery disease could not be distinguished qualitatively from maps of normal subjects on visual evaluation. However, a comparison of the average map for all coronary disease patients with the average normal map demonstrated some differences (figure 1). Selected map frames from the early, mid, and late QRS interval and early, mid, and late ST-T interval are shown. During the QRS, the null or zero potential line separating positive from negative potential on the anterior thorax was more vertical on the average map for patients with coronary disease than on the average map for normal subjects. As in the study by Stilli et al.,10 we found the average map from patients with coronary artery disease had lower maximum ST segment potentials than nor-

<table>
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<tr>
<th>Clinical diagnosis</th>
<th>Map diagnosis</th>
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<tr>
<td>Coronary disease</td>
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<tr>
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the average maps at those times and this was true of the entire first and last thirds of the QRS interval. The most significant feature differences between the two average maps occurred during the middle third of the QRS interval and these are shown in frames 33, 41, 49, and 57 (figure 2). The most prominent difference was a decrease in potentials around the entire lower thorax and an increase in potentials in the anterior superior thorax. During the ST-T interval, patients with coronary disease, on average, tended to have decreased anterior potentials compared with normal subjects. Overall distribution of T potentials was similar on the two average maps. Since few potential lines were present in the feature difference map during the ST-T interval, these map frames were not illustrated.

Figure 3 displays map frames from the midportion of the QRS interval on average maps from the three different single-vessel coronary artery disease groups. Frames from average maps for three patients with isolated right coronary artery disease, eight patients with isolated left anterior descending coronary artery disease, and four patients with isolated circumflex coronary artery disease are shown in columns 1 to 3. Frame numbers in column 1 refer to times in milliseconds from the beginning of the time-normalized QRS interval. In frame 21 there was an increase in the amplitude of the anterior maximum on the average map for the left anterior descending disease group compared with the right coronary artery disease group. The average map of the circumflex coronary artery disease group showed even higher amplitude of the maximum and a larger distribution area of positive potentials at this time than either the left anterior descending or right coronary artery disease group. Frames labeled 41, 20 msec later, were similar in the groups. There was a more vertical null or zero potential line anteriorly and more extensive distribution of negative potentials on the average map from the circumflex artery disease than on the average maps for the other groups. In frame 53, the amplitude of the minimum was greater on the average maps from the left anterior descending and circumflex artery disease groups than the average map from the right coronary disease group. The region of negative potentials was distributed more extensively over the inferior and posterior thorax on the average map from the circumflex artery disease group than on the other two average maps.

The average difference maps between average maps for each single-vessel disease group and the average map for normal subjects were obtained by subtraction of an average normal map from the average map for each single-vessel disease group. These average dif-
CAD - NORMAL

QRS INTERVAL

FIGURE 2. A feature difference map computed by subtracting statistically different map coefficients in an average normal map from an average map for patients with coronary disease. Map frames are displayed in the same manner and scale as figure 1. Lack of isopotential lines indicates statistical differences were few during the time of those map frames.

Difference maps are shown in Figure 4. The first column is the average map for the right coronary artery disease group minus the average normal map, the second column is left anterior descending disease map minus normal, and the third column is the circumflex artery disease map minus normal. The numbers listed on the left are the time in milliseconds from the beginning of the QRS and they are the same as in Figure 3. Each of the three time frames of the difference maps had distinctive amplitudes and distributions of maxima and minima. The most distinctive patterns of the difference maps were seen in frame 53. The region of negativity in the right coronary artery disease minus normal map was anterior, rightward, and inferior. In the left anterior disease minus normal map the region of negativity was anterior, leftward, and inferior and in the circumflex artery disease minus normal map, the region of negative potential was inferior around the entire thorax. Distinctive differences in positive potentials were also apparent in the three difference maps during frame 53.

ST-T potentials in each of the three difference maps shown in Figure 4 were less distinctive and are not illustrated. The major difference between the average T map for each single-vessel coronary disease group and the average map for the normal group map was a decrease in the amplitude of T potentials on the average maps for the three single-vessel disease groups.

Discussion

This study extends previously reported observations with the use of body surface mapping in patients with coronary artery disease and normal 12-lead electrocardiograms. An early related study by Kornreich et al. showed that multivariate statistical analysis of the orthogonal electrocardiogram correctly identified only 49% of patients with coronary artery diseases. When a selected set of nine leads previously shown to provide more waveform information was used, 79% of patients with coronary disease were shown to have QRS interval abnormalities and were correctly classified as having coronary artery disease. A later body surface mapping study by De Ambroggi et al. described qualitative abnormalities of the minimum potential recorded during the ST interval in 52% of a group of 25 patients with coronary disease. A recent study by Stilli et al. reported a 91% correct classification of maps from patients with coronary disease and normal subjects with the use of multivariate statistical analysis of map potentials during the ST-T interval. We used a quantitative comparison of map potential amplitudes and
distributions as they vary with time during the entire QRST interval. This represents a quantitative evaluation of a much greater volume of electrophysiologic information available from the body surface and is the likely reason for the higher rate of accuracy compared with that in previous studies. While this study does not provide evidence that the map features found in patients with coronary artery disease are unique to coronary artery disease, statistical comparison with such a large normal population does suggest that the abnormal map

**FIGURE 3.** Average maps for each single-vessel coronary disease group. Each patient had only single-vessel disease of the type indicated. Frame numbers refer to time in milliseconds from the beginning of the QRS interval. Maps are displayed as in figure 1 with the same scale. Right = right coronary artery disease group; LAD = left anterior descending coronary artery disease group; Circ = circumflex coronary artery disease group.

**FIGURE 4.** Subtraction maps computed by subtraction of all coefficients of an average normal map from each of the average maps for the single-vessel disease group. Frame numbers are the same as in figure 3 and refer to time in milliseconds from the beginning of the QRS interval. Maps are displayed as in figure 1. Abbreviations are as in figure 3.
features identified are more likely to be due to coronary artery disease than to normal variation. It is important to note that visual analysis of body surface maps from patients with coronary disease was not diagnostically useful.

In this study, we found different average map patterns for each of three types of single-vessel coronary artery disease. The number of patients in each single-vessel group was small and statistical significance of the differences is uncertain. The average maps differed not only from each other but each single-vessel disease average map differed distinctively from an average normal map. This finding is clinical evidence of the regional sensitivity of body surface mapping. Additional clinical evidence of the regional sensitivity of body surface mapping has been provided in the study of Faugere et al.\(^5\) which showed that there is a spatial distribution of late ventricular potentials in patients with ventricular tachycardia, and by the study of Musso et al.\(^5\) which showed that body surface mapping could be used to diagnose myocardial infarction in the setting of left bundle branch block.

The body surface maps recorded from the patients in this study were all recorded during a resting, pain-free state. The distinction between normal and coronary artery disease was not based on ST segment displacement such as occurs during transient episodes of painless ischemia, although abnormalities of ventricular repolarization were apparent on the average map for patients with coronary artery disease when compared with the average map for normal subjects. The major portion of discriminating information used to separate patients from normal subjects was recorded during the QRS interval, the portion of the maps less likely to be affected by functional abnormalities known to cause nonspecific ST-T abnormalities on standard electrocardiograms. The electrophysiologic basis of the abnormalities detected in this study is uncertain. It is unlikely to be related to myocardial infarction in the usual sense since most patients had no clinical history of myocardial infarction and a majority of the patients had normal ventriculograms during catheterization. The possibility of microscopic foci of infarction cannot be excluded and such foci may have in fact been present. Histopathologic or cellular electrophysiologic studies from a group of patients comparable to those in this study are not available and the cellular effects of repeated episodes of transient ischemia in humans are not known. In microelectrode studies of chronically ischemic human and infarcted canine myocardium, increased cellular coupling resistance and action potentials with decreased resting membrane potential, amplitude, and maximal upstroke velocity have been reported.\(^{19,20}\) Any or all of these factors could contribute to abnormalities of ventricular activation and recovery detected in this study.

Although the map coefficients used to discriminate between patients with coronary artery disease and normal subjects can be identified as occurring during the QRS or ST-T interval, it is not possible to relate a specific physiologic basis for a given coefficient. The 216 coefficients calculated to represent each map and used to perform statistical comparison of map features are not themselves physiologic variables.

The uniqueness of the features used to discriminate the maps of patients with coronary disease is unknown. An arbitrary number of features was used in the classification and was less than 50% of the number of patients in the smaller group compared. To determine map coefficients unique to the diagnosis of coronary artery disease, it would be necessary to enlarge the disease group sufficiently such that the coefficients selected as most different from normal map coefficients no longer changed with addition of more patient maps. The next step would be to enlarge the classification process to include maps of patients with documented cardiac pathology different from coronary artery disease.

Clearly the patients with coronary artery disease in this study constituted a group with a predictable high prevalence of disease. The group consisted of mostly middle-aged men with chest pain of a type that prompted referral for coronary angiography. Such a group does not provide a rigorous test of body surface mapping as a screening test for coronary artery disease nor does the group cover the spectrum of coronary disease patients. However, all patients with coronary disease had normal 12-lead electrocardiograms and all maps were recorded at rest when subjects were asymptomatic with no recorded ST segment abnormalities of the type usually associated with ischemia. The presence of electrophysiologic abnormalities on body surface maps recorded under these conditions suggests multivariate statistical analysis of body surface maps may have potential as a screening tool for coronary artery disease.

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