The Missing Waveform Information in the Orthogonal Electrocardiogram (Frank Leads)

III. Computer Diagnosis of Angina Pectoris from “Maximal” QRS Surface Waveform Information At Rest

By F. Kornreich, M.D., P. Block, M.D. and D. Brismee, Ph.D.

SUMMARY

Nine surface electrocardiograms recorded on the thoracic surface at fixed and identical locations in 412 individuals were found to account for the maximal useful waveform information available in each individual. In other words, nine waveforms were capable of resynthesizing any waveform recorded on their thoracic surface. These nine waveforms were then submitted to multivariate statistical procedures and their diagnostic performance compared to the Frank leads on which the same procedures were applied. Before the data were fed into the computer, all waveforms were time-normalized and divided into eight equal parts, yielding 72 variables and 24 variables for the nine lead system and the Frank leads, respectively, for each individual.

In this paper we attempted to discriminate between normal subjects and patients with documented angina pectoris (typical history and positive coronary angiography); myocardial infarction was excluded in these patients. Only the resting QRS complex was considered. With the 9-lead system, keeping the specificity (true negatives) at 90%, the sensitivity (true positives) is 76%; with the Frank leads, the same specificity yielded a sensitivity of 49%. The repeatability of the results on new independent controls was also found very satisfactory.

The discrimination between patients with angina pectoris on one hand and left ventricular hypertrophy and myocardial infarction on the other hand resulted in a performance level of 89% and 87%, respectively, for the 9-lead system. A good correlation was also found between the extent of the coronary lesions (number of coronary vessels involved) and the fraction of correctly diagnosed patients.

The present study concluded that the retrieval of more complete surface information results in an evident improvement of the diagnostic performance of electrocardiography.

Additional Indexing Words:

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Angina pectoris  Biomedical Computer Programs  Discriminant function
Maximal surface waveform information  Missing information  Multivariate analysis
QRS-complex at rest  Microinfarctions  Myocardial scars

IT IS NOW GENERALLY RECOGNIZED that the standard 12-lead ECG at rest and the Frank leads often are of limited help for the diagnosis of coronary arterial obstructive disease and uncomplicated angina pectoris. Indeed, almost half of such patients are found to have normal recordings.3, 4 Although undoubtedly the exercise electrocardiogram has improved diagnosis accuracy, the number of “normal” recordings in these cases is still too high.3, 4

Most electrocardiographic studies of angina pectoris have focused mainly on the ST-T wave changes since the QRS complex was found to exhibit only unspecific abnormalities1, 2, 5 which could not be routinely used to assess the diagnosis of coronary artery disease in the absence of recognizable myocardial infarction. Clinopathological and electrocardiographical studies however revealed small amounts of necrosis or fibrosis had occurred6, 7, 8, 9, 10, 11 in patients suffering typical angina pectoris but without clinical, biological, or ECG evidence of myocardial infarction; similar studies also showed a close relationship between appearance of scars too small to produce clinical, biological, or ECG evidence of myocardial infarction and QRS changes such as high-frequency components12, 13, 14, 15, 16, 17, 18, 19, 20 or amplitude modifications6, 21, 22, 23. These findings stress
the fact that QRS changes that are lost in routine ECG recordings can be retrieved provided the proper recording technique is used, e.g., high fidelity, high-speed recordings to disclose high frequency components.

Another limitation in the routine ECG diagnosis is that neither the 12-lead ECG nor the orthogonal corrected 3-lead system makes use of all the information available on the body surface. In that respect, with particular reference to coronary artery disease, we cite recent work on isopotential maps describing abnormal surface potential distribution, not reflected in the standard 12-lead ECG.

In a previous paper a lead system, consisting of nine unweighted surface leads, was designed, accounting for the maximal significant waveform information. These nine waveforms, recorded at identical anatomical sites in each patient, were fed into a computer and subjected to multivariate statistical procedures, similar to those extensively described by Pipberger. The diagnostic results were compared with those obtained with the Frank leads. This paper describes the performance of the 9-lead system in angina pectoris using the same statistical procedures applied to the QRS complex at rest.

**Material and Methods**

The material consisted of 412 well-documented patients (Table 1); for each patient 126 surface electrocardiograms were available. All patients had undergone clinical evaluation, including chest X-ray and ECG. The patients with a negative history, a normal physical examination, as well as a normal chest X-ray were included in the normal group. The ages of this group ranged from 20 to 50 years. The ECG was not taken into account for the assessment of normality (neither was it for the constitution of the other groups).

The angina pectoris group was composed of patients with a typical history of angina, defined as a pain, typical with respect to quality, location, duration and provocation by effort or stress. The group was then limited to only the patients with at least a 50% occlusion in one of the coronary vessels, as determined by angiography, and normal ventricular function by ventriculography. The patients with old or recent myocardial infarction, clinically and biologically assessed, hypertension, valvular disease, and congestive heart failure were excluded. A final series of 83 patients was built up, of which 55 constituted the learning group and 28 the control group. The learning group was further broken down by the number and site of coronary artery lesions resulting in respectively 9, 19, 19, and nine patients with one, two, three, or four (right coronary artery, left coronary artery, circumflex artery, and left main trunk) obstructed vessels. The ECG was not taken into account for the constitution of this group of 83 patients except for the exclusion of records with a QRS duration \( \geq 0.126 \) sec.

The diagnosis of left ventricular hypertrophy (LVH) was assessed on cardiac catheterization during which hemodynamic data and biplane angiograms were obtained, permitting the evaluation of LV volumes and muscle weights. LVH was defined as left ventricular muscle weight greater than two standard deviations above the mean LV muscle weight for adult male subjects, which is \( 188 \) g \( \pm 33 \) gr. The upper limit considered to be normal is thus \( 254 \) g. All patients with LVH had isolated aortic valve disease.

The myocardial infarction group consisted of patients with a typical history of infarction, characteristic enzyme changes at the onset, coronary occlusions and LV dysfunction in most cases as demonstrated by coronary angiography and ventriculography. Autopsies were performed on some patients. No classification as to the site of the myocardial infarction was attempted, all patients being pooled into one single group.

A fifth series of 34 patients with nonischemic chest pain and negative coronary arteriography was also considered in this study.

In each of the 412 patients, nine surface leads, recorded at the fixed anatomical positions, described previously and linearly combined, were found capable of resynthesizing the electrocardiograms recorded at 126 thoracic sites within the noise level. This 9-lead system accounts in each subject, for the maximal surface waveform information as defined previously.

In order to avoid an absolute time-scale, which does not permit the statistical comparison of identical parts of the ECG complexes, time-normalization was performed by dividing the QRS complex into eight equal parts, resulting in 72 variables for each individual. Identical time-normalization was performed on the Frank leads so that each subject could be represented by 24 variables.

The statistical procedures involved were described in detail in a previous paper. Briefly, the best discriminators were selected by stepwise discriminant analysis (Biomedical Computer Program 07M); these selected variables were then entered into another program (Biomedical Computer Program 04M) for the computation of the linear function \( L = X_1 \lambda_1 + X_2 \lambda_2 + \ldots + X_n \lambda_n \) in which \( n \) is the number of arbitrarily chosen variables and \( \lambda \) the corresponding coefficients.

**Results**

The differences between normals and patients with angina pectoris were assessed and then the angina group was successively compared with patients with LVH and patients with myocardial infarction. The number of variables selected through the BMD 07M

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**Table 1**

**Diagnostic Grouping of Study Patients**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>145</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>83</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>38</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>92</td>
</tr>
<tr>
<td>Chest pain (negative coronary angiography)</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>412</td>
</tr>
</tbody>
</table>

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program was 6, 6, and 8* for the comparison of angina to normal group, angina to LVH, and angina to myocardial infarction, respectively. The discriminators which proved best for differentiation between patients with angina and normal subjects, and were selected with the BMD 07 program, are depicted in figure 1. These variables were introduced in the BMD 04M program for the computation of the coefficients of the discriminant function. The results appear in table 2. The products of the coefficients, with the means of the variables, are also shown in table 2 because they indicated the true contribution to differentiation.

Table 3 gives the accuracy of classification (in percent) of patients with angina pectoris versus normal, LVH, and myocardial infarction, respectively, using the 9-lead system. For comparison, the classifications based on the Frank leads are also shown in table 3. The same number of discriminators was chosen for the Frank leads in order to make the performance of both systems entirely comparable.

A quantitative relationship between the severity of the coronary lesions and the value of the discriminant—

Figure 1

The electrode sites for the 9-lead system are indicated with large dots. The corresponding electrocardiograms are depicted: they are represented as time-normalized averaged QRS complexes divided into eight equal parts (the numbers in the abscissa indicate this division from 1/8 to 8/8). The solid lines represent the averaged normal QRS complexes and the dotted lines the averaged QRS complexes of the angina pectoris group. The vertical bars indicate the selected discriminators (see text and table 2). One can observe that the leads 1, 2, 3, 4, and 8 do not differentiate: in fact, discriminators exist for these leads, but are not retained because they are entered in the BMD 07M program beyond the decided cut-off level of six variables. Note that the variable on lead 5 does not look significantly different for the two groups: this is due to the fact that, first, the mean instantaneous QRS values do not really reflect the actual distributions which are not Gaussian, and second, this variable participates in the discrimination in combination with other variables.

For the determination of these numbers, two conditions were taken into account: first, no significant improvement of the differentiation was achieved beyond these levels, and second, the number of discriminators should not be too large because too many variables may lead to overly optimistic results which cannot be repeated on new and independent samples. 34, 35, 36, 37, 78

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Table 2

<table>
<thead>
<tr>
<th>Variables Which Proved Best for the Differentiation Between Normal Records and Those from Patients with Angina Pectoris</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-lead system</td>
</tr>
<tr>
<td><strong>Lead</strong></td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>

*Product of the coefficients and the averaged means of the normal and angina groups. These products indicate the true contribution to differentiation.**

Discussion

Limitations of the methods

There were two main limitations to this analysis. The first deals with the determination of a given number of surface leads which should account for the maximal waveform information; this number depends on the noise recorded in the original data. Improvement of the technical conditions could modify the number of waveforms needed to achieve satisfactory resynthesis of the original signals. The second limitation was the marginal size of the samples involved in the statistical procedures. As stated by the authors familiar with multivariate techniques, the results are only reliable when estimated from large populations. Therefore, the results shown in this paper need further confirmation on a larger population with angina pectoris and coronary angiography.

Differentiation between patients with angina pectoris, normal subjects, and patients of other groups

Composition of the series

The selection of patients with angina pectoris rests on a typical history of pain. The presence of occluded vessels as evaluated by coronary arteriography gives anatomical support to the diagnosis. Patients with a documented myocardial infarction (acute or remote), left ventricular hypertrophy, valvular disease and pulmonary involvement were excluded from this series. Electrocadiographic elements were not taken into account for the composition of the series except for the exclusion of recordings showing conduction defects (QRS duration ≥ 0.126 sec). It should also be stressed that only the QRS complex was analyzed in the present study. Angiographic findings of luminal narrowing of 30% or more in at least one vessel was required for inclusion in the angina group.

In the absence of available autopsy material for this group of 83 patients it is impossible to document

The ECG analysis was routinely performed in the ECG laboratory of the University Hospital by members of the Staff of Cardiology. The authors are indebted to Dr. J. Holt, Jr., for having provided these protocols.
whether or not microinfarctions have occurred during bouts of angina pectoris. However, clinico-pathological studies performed on comparable groups of patients\(^6,7,8,9,10,11\) reported a high occurrence of small infarction zones in the heart muscle, including subendocardial, septal, or intramural tissue. Moreover, the \textit{a posteriori} discovery of abnormal Q waves in three patients of the learning group lend support to the hypothesis that necrosis or fibrosis can be present without clinical, biological, and ventriculographic evidence of myocardial infarction in this series. The authors believe, however, that gross myocardial infarction has practically been eliminated from their group of patients classified as angina pectoris.

For the population of normal subjects based on a negative history and a normal clinical evaluation, no coronary arteriography was done. We consider this population as the normal reference although we are aware of the approximate character of this definition. Indeed, postmortem studies in clinically asymptomatic patients reveal atheromatous coronary disease in a nonnegligible fraction.\(^7,90,91\) However, although autopsy studies of combat casualties in the Korean War (age range: 18-48 years)\(^90\) and in the Vietnam War (age range: 18-37 years)\(^4\) showed atherosclerotic lesions in a large percentage of patients, the extent of the obstruction was significant in less than 5% of the cases only.

A small group of 34 patients with atypical or non-ischemic chest pain syndrome and negative coronary arteriography was also considered "normal" with

**Table 3**

*Accuracy of Classification of Diagnosis by 9-Lead and Frank Lead System*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>9-lead system</th>
<th>Frank leads</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correctly classified</td>
<td>Misclassified</td>
</tr>
<tr>
<td>Angina pectoris (55)</td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>Normals (100)</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Performance</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris (55)</td>
<td>88%</td>
<td>12%</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (58)</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Performance</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris (55)</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>Myocardial infarction (92)</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Performance</td>
<td>87%</td>
<td></td>
</tr>
</tbody>
</table>

Number in parenthesis = number of patients in group.

**Table 4**

*Classification of Patients with Angina Pectoris with Respect to the Number of Occluded Coronary Vessels (Occlusion \(\geq 50\%\))*

<table>
<thead>
<tr>
<th>No. of occluded coronary vessels</th>
<th>No. of patients</th>
<th>No. of patients classified as having angina*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9-lead system</td>
<td>Frank leads</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>5 (44%)</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>17 (89%)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>7 (89%)</td>
</tr>
</tbody>
</table>

*Classification based on the values of the linear discriminant function for each patient (specificity level 90%).
The data were prepared by time-normalizing the QRS complex and dividing it in eight equal parts. This procedure, proposed by Pipberger,33 was used by several authors dealing with coronary artery disease60, 61 and was particularly suitable for computer analysis as it achieved data reduction and defined each individual as a N-dimensional vector for subsequent multivariate analysis.
This patient also suffered typical angina pectoris without evidence of myocardial infarction. The standard 12-lead ECG was found borderline as far as ST-T is concerned. The Frank leads (QRS complex) were normal. In this subject, variables 7/8 QRS in lead 4, 4/8 QRS in lead 6, 4/8 and 7/8 QRS in lead 9 clearly have abnormal values; the patient was classified as 'angina pectoris' according to the value of his discriminant function, combining all the selected variables. See legend to figure 2 for explanation of the presentation of findings.

The number of variables chosen as best discriminators with the BMD 07M program and for entry into the BMD 04M program is dependent on the sample size and should not be too large because too many variables may lead to overly optimistic results which will not be repeated on new and independent samples. Therefore, a small number of variables was selected (six to eight) for each of the discriminant functions involved in this study (tables 2 and 3). Because of this constraint, discriminators entered in the BMD 07M program beyond this fixed cut-off level were not retained for the further computation of the discriminant functions although they could improve the differentiation.

Most of the variables which proved best for the differentiation between normal records and those patients with angina pectoris were found (for the 9-lead system) in the second half of the QRS complex; one of them was at the junction (J point) of QRS and the ST-T segment; this variable however has a relatively small weight in the discriminant function. Similar conclusions can be drawn for the Frank leads (table 2). Most of the QRS changes (7/8 lead 4, 6/8 lead 7, 4/8 lead 6, and 4/8 lead 9) indicated a decrease in the amplitude of the mean instantaneous voltages. Only variable 7/8 in lead 9 (in the back) represented an increase in voltage which might indicate a trend to ST-T elevation; similarly, variable 8/8 in lead 5 corresponds to a shift of the J point. More light may be shed on these aspects in a projected similar analysis of the ST-T wave.

Discussion of the diagnostic performance
A reliable and accurate comparison with the data

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published in the literature concerning electrocardiographic recognition of angina pectoris is a very hazardous undertaking because of differences in the makeup of series, choice of the diagnostic criteria, statistical procedures used, and the frequent absence of documentation by coronary angiography. Moreover, this particular paper dealt with the QRS complex only and explores the diagnostic performance at rest. In order to evaluate the diagnostic performance of the nine-lead system with respect to a classical, widely used lead system, the Frank leads were studied in the same groups using identical procedures on the QRS complex.

The comparability of our findings is based on the assumption that diagnosis findings based on Frank leads are interchangeable with findings from the standard 12-lead system. Various authors demonstrated reasonable interchangeability as far as clinical diagnosis is concerned between the orthogonal corrected leads and the standard 12-lead ECG.\textsuperscript{62, 63, 64} Therefore the findings in our comparison of the 9-lead system with the Frank leads can be used to assess the improvement in diagnostic performance of the proposed system with respect to a routine lead system.

**Differentiation between patients with angina pectoris and normal subjects.** Throughout all procedures the specificity level (correct negative diagnoses) was kept at 90% in order to compare with the average specificities reported in the literature\textsuperscript{65, 66, 67, 68} on series comparing stress ECG findings with coronary arteriographic data. At this specificity level, the sensitivities with the 9-lead system and the Frank leads reached 76% and 49%, respectively, resulting in a performance level (defined as the average of sensitivity + specificity) of 83% and 69%. Among the figures reported in the literature on series of patients with arteriographically documented coronary artery disease the resting ECG and/or VCG yielded performance levels which ranged from 52 to 76%.\textsuperscript{67, 68, 69, 70}

Unfortunately these reports included patients with angina pectoris as well as myocardial infarction, and it is not always clear whether or not the patients were selected on the basis of an abnormal ECG.

In a recent work,\textsuperscript{71} using multivariate analysis on QRS and T variables in a series of patients with coronary artery disease (including myocardial infarction) but without arteriographic data, the performance level achieved was 78%. The performances of course can be enhanced by the exercise ECG as apparent from figures ranging from 76 to 87%\textsuperscript{9, 72, 73, 74, 75} which include ST-T wave changes.

The results of the present study show that the performance levels of the Frank leads in our population came very close to those described in the literature for the resting ECG. The performance levels achieved with the nine-lead system at rest and on the QRS only compared with performance levels in tests on stress ECG series utilizing ST-T criteria. It should also be stressed that the standard 12-lead ECG of the 55 patients with angina pectoris, read by skilled cardiologists, yielded a positive result (abnormal ST-T) in only 40% of the records. It is therefore suggested that the 9-lead system described in this report should by no means replace exercise testing, but on the contrary, should be used in exercise testing and extended to analysis of the ST-T wave. The proposed approach could lead to a better selection of the electrode positioning for exercise ECG testing and hence improve its diagnostic performance.

The relationship between the extent of the coronary involvement and the sensitivity of the test (number of patients truly recognized) confirms a now generally admitted idea: the performance level increases as the number of coronary vessels occluded increases (table 4). This trend holds true for the 9-lead system with more than three vessels occluded but fails for the Frank leads: perhaps more definite conclusions can be drawn in a study of a larger number of patients.

**Differentiation between patients with angina pectoris and patients with left ventricular hypertrophy and myocardial infarction.** The higher sensitivity of the 9-lead system as compared to the Frank leads is evident (table 3) for the discrimination of these pathological groups too; the superiority of the 9-lead system is, however, less marked than when discrimination between normal subjects and patients with angina is looked for; this probably indicates that the 9-lead system exhibits its superiority mainly when small differences between two populations are involved. It is probable that the nine-lead method, by providing more complete electrical information for each patient, enhances the selection of discriminating variables.

**Tentative explanation for the mechanism of the QRS changes**

As stated above, small zones of necrosis or fibrosis might be responsible for subtle QRS changes which are not evidenced in routine ECG recording and analysis. Although no autopsy material was available in our series of angina pectoris patients, one can infer from numerous clinicopathological and electrocardiographical studies\textsuperscript{6, 7, 8, 9, 10, 11} that such microinfarctions or scars most certainly exist in a large fraction of our patients. Whether QRS changes in these patients can be produced only by actual scars or whether other
had been divided in eight equal parts yielding a sampling incompatible with the study of high or even medium frequencies. Therefore the authors assumed that the QRS changes they observed were different from high-frequency components and mainly referred to amplitude changes at particular instants of the QRS complex. In that respect it is interesting to cite a recent paper of Simonson\(^9\) describing amplitude changes with age and ascribing them to asymptomatic coronary artery disease with progressive myocardial fibrosis.

Repeatability of the results on control groups

The discriminant function determined with respect to the normal test group of 100 clinically normal patients (without coronary arteriography) was tested on three new independent samples of normal and angina patients. The test on both normal groups controlled the specificity of the discriminant function; as already mentioned, both populations presented shortcomings; in the first group no real proof exists that their complaints were unrelated to heart disorders, and in the second, the absence of arteriography did not completely rule out the possibility of the presence of asymptomatic cardiac disease.

With these limitations in mind the comparison of tables 3 and 5 show that the repeatability for both systems was very good as far as the normal control group of 45 patients is concerned (88% vs 90% for the 9-lead system and 90% in both for the Frank leads). This repeatability is somewhat lower for the group of 34 patients with negative coronary angiography (85% for the 9-lead system and 82% for Frank leads) which raises the suspicion that some of these patients (within the limits of our methodology) might in fact have had myocardial ischemia with atypical complaints. As far as the control angina pectoris group was concerned, excellent repeatability was obtained for both lead systems (78 vs 76 (Frank leads) and 53 vs 49): the discrimination achieved in the control group was practically identical to the one observed in the learning group. Larger series are needed to confirm these results.

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