Publication II
Computer model analysis of the relation of ST-segment and ST/HR slope response to the constituents of the ischemic injury source
Computer Model Analysis of the Relationship of ST-Segment and ST-Segment/Heart Rate Slope Response to the Constituents of the Ischemic Injury Source

Jari Hyttinen, PhD,* Jari Viik,* Rami Lehtinen,* Robert Plonsey, PhD† and Jaakko Malmivuo, PhD*

Abstract: The objective of the study was to investigate a proposed linear relationship between the extent of myocardial ischemic injury and the ST-segment/heart rate (ST/HR) slope by computer simulation of the injury sources arising in exercise electrocardiographic (ECG) tests. The extent and location of the ischemic injury were simulated for both single- and multivessel coronary artery disease by use of an accurate source-volume conductor model which assumes a linear relationship between heart rate and extent of ischemia. The results indicated that in some cases the ST/HR slope in leads II, aVF, and especially V5, may be related to the extent of ischemia. However, the simulations demonstrated that neither the ST-segment deviation nor the ST/HR slope was directly proportional to either the area of the ischemic boundary or the number of vessels occluded. Furthermore, in multivessel coronary artery disease, the temporal and spatial diversity of the generated multiple injury sources distorted the presumed linearity between ST-segment deviation and heart rate. It was concluded that the ST/HR slope and ST-segment deviation of the 12-lead ECG are not able to indicate extent of ischemic injury or number of vessels occluded. Key words: ischemia, ST-segment deviation, ST-segment/heart rate slope, modeling, finite difference element method.

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The use of modern signal processing and analysis methods with improved parameters, especially those based on heart rate (HR) adjustment of ST-segment depression, such as the ST/HR slope (1,2) and ST/HR analysis (3,4), have considerably improved the diagnosis of coronary artery disease (CAD). The ST-segment, and especially the ST-segment as a function of HR, may provide information regarding the ischemic injury source, such as the extent and location of the injury and the number...
of vessels obstructed. This information could be very important when deciding on possible further tests and the prognosis and treatment for a patient. Theoretical considerations based on the solid angle approach and experimental evidence of ST-segment and ST/HR slope response to the constituents of the injury have been presented (2,5-7). The good performance of ST/HR analysis has been postulated to arise from the expectation that the ST/HR slope should be directly proportional to the area of the ischemic boundary during transient ischemia associated with exercise (2,9).

The foundation of these conclusions, the solid angle theory, is based on the assumption that the human thorax can be described as a homogeneous unbounded volume conductor (10). This model, however, may not provide all the important aspects that affect the ST-segment response and thus may limit the interpretation of electrocardiographic (ECG) measurements and the diagnosis of CAD. In a human thorax, the resistive inhomogeneities and the boundary of the thorax (ie, the constituents of the volume conductor), affect the measured ECG signal. In addition, in multivessel CAD the obstructed vessels most probably differ in their capability to supply blood, thus producing complex and multiple source areas. Thus, the relationship of ST-segment depression and ST/HR slope to the extent of the ischemic lesion or the number of diseased vessels may not be as straightforward as is stated in terms of the simple solid angle approach. Owing to the complexity of the myocardial electrophyslogic changes and interpatient variations, this information may be difficult to determine on the basis of routine clinical measurements.

The main aim of this computer model study was to determine the relationship between the ST-segment parameters and the features of ischemic injury. The presumed linear relationship between the extent of ischemia and the ST/HR slope was studied in detail, and simulations were carried out for the case of single and multivessel CAD. This article describes an application of an accurate source-volume conductor model to the theoretical evaluation and analysis of the ST-segment deviation and ST/HR slope arising from the exercise ECG.

**Methods**

The theoretical basis of a double-layer model of an ischemic injury source in the analysis of ST-segment and ST/HR slope, which follows the framework suggested by Okin and Kligfield (2,4). The analysis is based on experimental evidence and on the solid angle approach (2,9). We extended the concept of Okin and Kligfield by including the effects of the constituents of the volume conductor and the basic factors arising in multivessel CAD.

**Theoretical and Experimental Basis for Modeling of Ischemic Injury Sources Producing ST-Segment Deviation**

**Theoretical Basis of ST-Segment and ST/HR Slope Analysis Based on Solid Angle Approach.** According to experimental evidence, the changes in the heart's electrochemical function in CAD produce a potential difference between the contiguous healthy and ischemic cells, which generates an injury current between the aforementioned regions, resulting in an ST-segment deviation (7,11). It has been proposed, on the basis of experimental and theoretical studies, that this injury source can be modeled as a double-layer source lying on the border of the ischemic and healthy myocardial regions, assuming uniform tissue on either side (5,6,8,12,13).

ST-segment analysis based on a solid angle approach states that in an unbounded homogeneous volume conductor, the relationship between the recorded ST-segment deviation of an ECG lead (ΔST_l) and the spatial (solid angle Ω_s) and nonspatial (ΔV_m, difference of transmembrane potentials between adjacent muscle regions) properties of the ischemic injury source is described by the equation

\[
ΔST_l = (Ω_s/4π)ΔV_mK
\]

where the factor K corrects the difference between intracellular and extracellular conductivity and changes in gap-junctional conductance (6). The factor ΔV_m includes the resting membrane potential difference (true ST-segment change) and TP-segment changes of the myocardial action potential. These changes combined form the ST-segment deviation of the surface ECG (5,14).

Although ST-segment deviation is affected by these factors, a simplifying parameter has been proposed based on the concept of ST/HR slope. The latter, in turn, is evaluated on the basis of the following assumptions suggested by Okin and Kligfield (2). The spatial extent of the source remains practically constant after the ischemic region is established at an early stage of ischemia (2). Thus, the source is spatially stationary and the solid angle Ω_s will not change. When ischemia deepens, only the nonspatial variables (ΔV_m) change. This notion does not have to hold throughout the entire exercise test but must hold at the time the ST/HR slope is determined. Furthermore, since HR is
assumed to be related to the oxygen demand of the myocardium and, after the hypoxia starts, to the metabolic depth of ischemia, $ΔHR$ is assumed proportional to $ΔV_m$. Thus, equation (1) can be now written as

$$\frac{ΔST}{ΔHR} = Ω_r C$$

where $C$ is a new constant describing the linear relationship between HR and depth of ischemia (2). The constants $K$ and $1/4\pi \tau$ are combined in constant $C$, and thus equation (2) is valid under conditions in which changes in conductance are proportional or small (2). This relationship reveals that the area of the ischemic boundary—that is the double-layer source—may be proportional to the ST/HR slope, as stated by Okin and Kligfield (2).

**Extension of the Elementary Solid Angle Approach: Effects of the Constituents of the Volume Conductor and Multivessel Coronary Artery Disease.** An extension of the solid angle approach, based on the simplified model presented by Okin and Kligfield to explain the theoretical basis of the ST/HR slope (2), includes the effects of the volume conductor constituents and the characteristics of the source or multiple sources in multivessel CAD disease. These factors may distort the conclusions regarding the relationship of the ST-segment and the ST/HR response to the extent and location of the ischemic injury.

The ischemic injury source produced by an occlusion in a single coronary artery may be assumed to be spatially stationary, as suggested by Okin and Kligfield (2). However, in the case of multivessel CAD, the size and location of the occlusions in each coronary artery are different, and thus the onset (HR level) of ischemia is bound to be different for each source as is the ST/HR relationship of each source after the onset of ischemia. Therefore, in multivessel disease there exist multiple sources at different locations in the myocardium with different temporal properties.

The solid angle of a double-layer source subtended from the measuring electrode does not provide an accurate transfer function from the source to the electric potential of the body surface. The boundary of the thorax and the inhomogeneities of various organs affect the electric field generated by the myocardial sources. In addition, the transfer function is distinctive for each source and ECG electrode configuration (15-18).

When the constituents of the volume conductor and the effects of multiple ischemic sources are considered, the equation for measured ST-segment deviation can be stated as

$$ΔST_l = \sum_n T_l n \cdot A_n K_m ΔV_{mn} (t_n - HR)$$

where $T_l$ is the transfer function from the ischemic source to the ECG lead $L$. It includes the effects of the constituents of the volume conductor on the measured ST-segment potential. This transfer function can be solved by using accurate models of the human thorax as a volume conductor. The terms $A_n$ and $K_m ΔV_{mn}(t_n - HR)$ correspond to the spatial (area) and temporal properties of source region $n$. Ischemia and the source $n$ are established at a certain HR level $t_n$. The spatial and temporal properties of the source model can be varied according to the simulation procedure. Equation (3) reveals that the recorded ST-segment potential reflects various factors, which emphasizes the need for more accurate analysis of the ST/HR relation.

**Realization of the Volume Conductor Model**

An accurate computer model of the thorax as a volume conductor was constructed on the basis of the finite difference method (19,20). The torso geometry was constructed from a digitized computed tomography scan with 10 mm spacing obtained from a 40-year-old man. The model comprised 91,282 elements defined by a nonuniform rectangular grid. In the heart region the resolution of the grid was 5 mm, increasing to 10 mm farther from the heart. In the heart region extra layers were interpolated between those obtained from computed tomography or magnetic resonance images to provide the 5-mm accuracy.

The lungs, spine, sternum, heart, aorta, and intracavitary blood masses were included in the model. The resistivities employed are listed in Table 1. Subcutaneous fat, skeletal muscle, and other regions of the thorax not listed in the table were considered to constitute a homogeneous structure coded as thorax. The heart resistivity represented domain properties of the cardiac syn-

<table>
<thead>
<tr>
<th>Inhomogeneity*</th>
<th>Resistivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone (spine, sternum, ribs)</td>
<td>16,000 Ω·cm</td>
</tr>
<tr>
<td>Lungs</td>
<td>2,100 Ω·cm</td>
</tr>
<tr>
<td>Blood (intracardiac blood mass, great veins)</td>
<td>160 Ω·cm</td>
</tr>
<tr>
<td>Heart muscle</td>
<td>380 Ω·cm</td>
</tr>
<tr>
<td>Thorax</td>
<td>460 Ω·cm</td>
</tr>
</tbody>
</table>

* All inhomogeneities are considered isotropic. Blood and bone resistance values from Geddes and Baker (37); other resistance values from Rush et al. (36).
cytium. All inhomogeneities modeled were isotropic. The finite difference method solver calculated the potentials and currents throughout the volume conductor generated by injury sources located in the myocardium.

Realization of the Double-Layer Source Model Generating ST-Segment Deviation and ST/HR Slope

Simulation of Localized Injury Sources. If it is postulated that, as assumed by Okin and Kligfield, the ischemic region is established at a very early stage of ischemia, and a subendocardial nontransmural ischemia is induced during the exercise test (2), a subendocardial, stationary, radially oriented double-layer source can be used to simulate the ischemic ST-segment injury sources throughout the test. To simplify and normalize the model, the strength of the layer may be assumed to be uniform, and thus a homogeneous double layer can be employed.

A homogeneous, subendocardial, stationary, radially-oriented double-layer source was used to simulate ischemic ST-segment injury sources. Double-layer sources were defined within the myocardial region of the thorax model in the anterior, lateral, inferior, posterior, septal, and apical sections of the endocardium of the left ventricle (Fig. 1). The endocardial nodes of each section represented the first (ischemic) layer, and the next layer of nodes toward the epicardium represented the second (healthy) layer. The second layer was located one grid space from the first in the direction of the epicardium. The separation between the adjacent layers of the source was 5 mm, and the area of each double layer was approximately 900 mm². Figure 2 illustrates the location of the nodes of an anterior double-layer source and the resolution of the model grid in a transverse slice of the thorax at approximately the middle of the left ventricle level.

Larger ischemic sources were formed by combining the effects of the regional sources described above. Because of the linearity of the source-volume conductor problem, potentials generated by larger sources can be obtained by adding the potentials generated by smaller regional sources. Anteroseptal-apical and posteroinferior sources were formed representing the regions supplied by the left anterior descending coronary artery and the right coronary artery, respectively. The lateral source represented the region supplied by the left circumflex coronary artery. Accordingly, ST-segments generated by multivessel diseases were obtained.

The ST-segment deviation was determined from the change of the ST-segment relative to the baseline of the measurement constituting the effects of injury source during both the ST- and TQ-segments. The strength of the source depends on the metabolic extent of ischemia. In this simulation study, a double-layer source strength of 65 mV was used, representing a source that might arise at the end of an exercise ECG test (7,11).

Simulation of the ST/HR Slope. As presented above, it was assumed that only the source strength of the injury source changes during the exercise test (2). Thus, the calculated ST-segment deviations also reflect the relative values or the distribution of the ST/HR slopes in the 12-lead ECG generated by the sources. However, the absolute value of the ST/HR slope depends on many factors (eg, the response of HR to the increased metabolic extent of ischemia).

The ST-segment deviations incorporate the ST/HR slopes in case of single-vessel CAD and in the case of multivessel CAD, providing that the temporal properties of the regional sources are considered identical. The calculated ST-segments induced by a 65-mV injury double layer can be considered to constitute a transfer function. The
ST/HR slope can be obtained by changing the source strength according to a postulated relationship between HR and ΔV_m. The source strength as a function of HR was considered linear (2), and the relationship was the same for all the sources. In the simulations of the ST/HR slope, the source strength ΔV_m was varied from zero to 65 mV as a function of HR, and the maximal strength, 65 mV, was achieved when HR had increased by 50 beats/min from the onset of ischemia.

The effect of the temporal properties of the sources on the ST/HR relation in multivessel CAD was modeled by using a different HR level for the onset of ischemia (ie, different τ_i for each source area n (equation 3)).

**Results**

**Relationship of the ST-Segment Deviation and ST/HR Slope to the Extent and Location of Ischemic Injury**

The ST-segment deviations in the 12-lead ECG generated by simulated sources are listed in Table 2 and shown as radar lead direction presentations in Figure 3; the axes have been aligned with standard

**Table 2. ST-Segment Deviation (mV) Generated by Localized Injury Sources and Combined Sources**

<table>
<thead>
<tr>
<th>Lead</th>
<th>Localized Injury Sources</th>
<th>One-Vessel Disease</th>
<th>Two-Vessel Disease</th>
<th>Three-Vessel Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior</td>
<td>Lateral</td>
<td>Inferior</td>
<td>Posterior</td>
</tr>
<tr>
<td>I</td>
<td>-0.01</td>
<td>-0.12</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>II</td>
<td>0.01</td>
<td>-0.04</td>
<td>-0.24</td>
<td>-0.01</td>
</tr>
<tr>
<td>III</td>
<td>0.02</td>
<td>0.08</td>
<td>-0.26</td>
<td>-0.02</td>
</tr>
<tr>
<td>aVR</td>
<td>0.00</td>
<td>0.08</td>
<td>0.11</td>
<td>0.02</td>
</tr>
<tr>
<td>aVL</td>
<td>-0.02</td>
<td>-0.10</td>
<td>0.14</td>
<td>0.01</td>
</tr>
<tr>
<td>aVF</td>
<td>0.01</td>
<td>0.02</td>
<td>-0.25</td>
<td>-0.02</td>
</tr>
<tr>
<td>V1</td>
<td>-0.17</td>
<td>0.09</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>V2</td>
<td>-0.62</td>
<td>-0.02</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>V3</td>
<td>-0.45</td>
<td>-0.07</td>
<td>0.11</td>
<td>0.16</td>
</tr>
<tr>
<td>V4</td>
<td>-0.12</td>
<td>-0.08</td>
<td>-0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>V5</td>
<td>-0.02</td>
<td>-0.09</td>
<td>-0.09</td>
<td>0.02</td>
</tr>
<tr>
<td>V6</td>
<td>0.01</td>
<td>-0.08</td>
<td>-0.09</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

* Combined sources represent LAD, LCX, and RCA regional sources, two-vessel disease LAD + LCX, LAD + RCA, and LAD + LCX, as well as three-vessel disease, LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery.
led directions in the frontal and transverse views. The values are given in millivolts and were calculated by using 65-mV double-layer injury sources and the finite difference thorax model.

The ST-segment deviations that incorporate the values of the ST/HR slopes on the 12-lead ECG generated by simulated localized injury sources are presented in Figure 3A. Almost all the areas generated an ST-segment depression of 0.10 mV or greater in lead $V_4$, $V_5$, or $V_6$. The posterior source generated reciprocal changes (ie, resulting in ST-segment elevation) in all leads except limb leads I, II, III, aVF, and $V_6$, where a very small ST-segment depression was observed. Inferior and apical sources generated similar patterns in the limb leads, resulting in large depressions in leads II, III,
and aVF. The septal source indicated significant ST-segment depression only in leads III and V₁. The lateral source was detected by almost all leads as an ST-segment depression, lead 1 having the largest depression. The anterior source was detected by ST-segment depression in chest leads V₁-V₃. The anterior and posterior sources generated very small potentials in limb leads.

Figure 3B illustrates ST-segments (and relative ST/HR slopes) of the 12-lead ECG generated by proximal one-lead CAD. The sources demonstrated anoreospetal-apical, lateral, and postero-inferior diseases, representing areas supplied by the left anterior descending, left circumflex, and right coronary arteries, respectively. Figure 3C indicates the responses of the three cases of two-lead diseases (left anterior descending + left circumflex, left anterior descending + right and left circumflex + right coronary arteries) and of three-lead disease.

ST-segment depressions were mostly generated by sources in the left anterior descending artery region, and ST-segment elevations, (reciprocal ST-segment depression), were generated by the right coronary artery sources (Fig. 3B and C). Leads V₄, V₅, and V₆ as well as leads II, III, and aVF detected most source configurations if the standard criterion of 0.10 mV or greater ST-segment depression was considered as an indication of ischemia. The increased extent of injury from a regional source to one, two, and finally three-lead disease gave rise to various changes resulting from changes in the geometry of the source and the location of the recording lead.

Figure 4 illustrates the relationship between the ST-segment deviation or the relative value of the ST/HR slope and the extent of the ischemic lesion. This figure indicates the ST-segment deviations of leads I, II, V₁, and V₃ and the maximal ST-segment depression of the 12-lead ECG in the four injury source categories: six localized ischemic sources and the three cases of one-lead, three of two-lead, and one of three-lead CAD. In addition, the average and range of the ST-segment deviations generated by the different source configurations are presented.

Figure 4 demonstrates that the average ST-segment response was directly proportional to the number of vessels occluded. In addition to the leads presented here, this was valid for all the leads of the 12-lead ECG. On the other hand, linear regression analysis indicated that the number of vessels occluded and the ST-segment value (which incorporate the ST/HR slope) had low likelihood of a linear relationship except in lead II (r > .553, P < .05) and leads aVF and V₅ (r > .456, P < .1). Furthermore even in leads II, aVF, and V₅, the range of the responses was large, and the number of vessels or the size of the source could not be classified on the basis of the ST-segment response.

ST/HR Relation in Single and Multivessel Coronary Artery Disease

In Figures 3 and 4 the ability of different vessels to supply the myocardial areas is considered to be equal (ie, the ST-segment potentials of the sources are simply combined). The coefficients Δ Vₘ, Kₚ, and τᵣ (equation 3) were considered similar for all the ischemic lesions. Figure 5 illustrates the ST/HR response in leads I, V₂, and V₅ to increased extent of ischemia and the response to varying characteristics of the sources produced by different occlusions in the coronary arteries. Figure 5A illustrates the ST/HR function generated by one-lead CAD, Figure 5A, F, and H that generated by two-lead CAD with similar occlusions in the vessels, and Figure 5E, G, and I that generated by two-lead CAD with different occlusions in the arteries. In the case of different occlusions, the ischemic changes were initiated at a different level of HR, which is described by the coefficient τᵣ in equation 3. In all the cases the relationship between HR and Δ Vₘ was considered identical. It is emphasized that Figure 5 represents one hypothetical example. Other levels of HR where different areas become ischemic are possible, as well as other coefficients describing the relationship between HR and Δ Vₘ.

Figures 3, 4, and 5 indicate that larger ischemic sources produce various responses depending on the source geometry and the ECG lead employed. Furthermore, the linearity of the ST/HR relation (Fig. 5) depends on the source geometry and the capabilities of the detecting lead. For example, in a left anterior descending + right coronary disease, lead V₂ indicated a nonlinear ST/HR relation, detecting ischemia of the right coronary artery disease as ST-segment elevation and that of left anterior descending artery disease as ST-segment depression (Fig. 5e). In left circumflex + right coronary artery disease, lead 1 showed a linear ST/HR slope (Fig. 5i) because it did not indicate the right coronary artery disease. In left anterior descending + left circumflex artery disease (Fig. 5i) lead V₅ detected mainly disease of the left anterior descending artery, and a large ST/HR slope induced at a high level of exercise was observed. Lead V₅ indicated all source areas as an ST-segment depression, producing ST/HR relations that appeared somewhat linear in all cases.
**Discussion**

**Clinical Observations Versus Simulation Results**

Our results are supported by many clinical observations. Leads $V_4$ and $V_5$ have been observed to provide the best performance in ischemia diagnosis (21). Our simulations demonstrated that lead $V_4$ and especially lead $V_2$ generally indicated a 0.10 mV or somewhat larger ST-segment depression (Figs. 3 and 4). Only posterior and septal sources produced ST-segment elevation. Thus, the criterion of ST-segment depression of at least 0.10 mV for positive diagnosis performs well in these leads. Other leads may require different criteria adjusted to the properties of the lead, as has been observed in clinical studies (22).
Fuchs et al. (23) have found that in patients with single-vessel CAD, mirroring changes are more often observed in right coronary and left circumflex artery disease (88% and 80%, respectively) than in left anterior descending artery disease (39%). In the areas perfused by the right coronary

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**Fig. 5.** Illustrative demonstration of ST/heart rate relations in single- and multivessel disease. ST/HR relations of leads I, V2, and V5 generated by double-layer subendocardial ischemic injury sources: (a) LAD source; (b) LCX source; (c) RCA source, single-vessel disease; (d), (f), and (g) sources representing two-vessel disease of LAD + LCX, LAD + RCA, and LCX + RCA, respectively, with similar occlusions in the vessels; (e), (g), and (i) sources representing two-vessel disease of LAD + LCX, LAD + RCA, and LCX + RCA, respectively. Different occlusions produce ischemia and injury sources at different heart rates. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery, RCA, right coronary artery.
and left circumflex arteries, the leads of the 12-lead ECG have more diverse sensitivity properties and both ST-segment depression and ST-segment elevation may be expected. Figures 3 and 4 indicate that left anterior descending coronary artery sources generated ST-segment depression in most of the leads, while right coronary artery sources particularly produced ST-segment elevation (ie, mirroring ST depression).

Detecting the Extent and Location of the Injury Source

Relationship of ST-Segment Deviation to Extent and Location of the Ischemic Injury. Each regional injury source generated a more or less distinct pattern of ST-segment deviation in the leads of the 12-lead ECG (Fig. 3). This suggests that the ST-segment may be useful in the localization of ischemia. However, clinical studies that have attempted to localize ischemia show that the ST-segment is not a useful classifier of the location (24–26). This finding supports the notion that ST-segment deviation is affected by both the spatial properties and the metabolic depth of ischemia (2) and furthermore that the latter affects each injury source differently. Thus ST-segment deviation alone cannot provide information regarding the constituents of the injury.

Relationship of the ST/HR Slope to the Extent of the Ischemic Injury. If the ischemic lesion remains spatially stable during the exercise test and HR is linearly proportional to the metabolic depth of ischemia as stated (2), the ST/HR slope and, in particular, the distribution of the ST/HR slope of the 12-lead ECG may give a more direct indication of the location and extent of ischemia. However, there are contrary indications. According to the solid angle theory, the solid angle seen from the measuring electrode is not linearly related to the area of the ischemic-healthy tissue boundary but rather to the opening of the double layer as seen from the electrode (10). Thus, in an approximately spherical organ such as the heart, a large ischemic area may cause a small opening of the double-layer cup and hence a smaller recorded potential than a small lesion. The situation becomes more complex when the effects of the volume conductor are also considered. On the other hand, clinical data may indicate a statistically significant linear relationship between the ST/HR slope and the number of vessels occluded, which is similar to the data represented in Figure 4. On the basis of the results presented here, leads II, aVF, and V₅ may be possible candidates for evaluating the extent of ischemia based on the ST/HR slope. These leads indicated most of the regional ischemias by ST-segment depression, thus responding to increased size of the territory by increased depression. Anterior sources were not detected by leads II and aVF, which decreases their ability in ischemia diagnosis. In particular, lead V₅ indicated the increased size of the ischemia by larger ST-segment depression providing that the ischemia was not in the septal section. This result manifests the clinical relevance of lead V₅ in stress testing. However, when an individual case is analyzed, the ST-segment potentials (or ST/HR slopes) may not indicate the extent of the ischemic injury as shown in Figures 3 and 4; the ST-segment response had practically no linear relationship to the extent of ischemia when the parameter is obtained from a single lead or the maximum value of the parameter is defined. In multivessel CAD, ST-segment depression may be lower than that produced by localized sources. In addition, the variance of clinical ST/HR slopes is further increased by interpatient anatomic differences. Therefore, the ST/HR slope may not directly reflect the extent of injury or the number of stenotic vessels, as has been proposed by Okin and Kligfield (2) and Elamin et al. (1), respectively.

ST/HR Relation in Multivessel Coronary Artery Disease. In addition, sources arising from multivessel CAD may affect the behavior of the ST/HR relation. Most probably, the maximum capacity of the obstructed vessels to supply blood to the myocardium is reached at different flow velocities and heart rates. This produces two ischemic regions, injury sources arising at different levels of exercise. Thus, in multivessel CAD, the spatial properties of the source are also prone to change. This phenomenon is shown in Figure 5. In the case of multivessel CAD, the linearity of the ST/HR relation depends on the constituents of the injury source and their relationship to the occlusions in the blood supply, as well as on the particular ECG lead. In addition, increasing nonlinearity will be generated by the relationship between HR and the metabolic extent of ischemia in different injury regions (ie, the value of HR in function of KₑAVₘₐₓ). This difference was not considered in this simulation study.

According to Okin and Kligfield, the linearity of the ST/HR slope is evident (9). This linearity may be due to the definition of the ST/HR slope and not due to the profound nature of the phenomenon. According to the definition, the steepest ST/HR slope (determined from the ST-segment depression)
Characteristics of the Source and Volume Conductor Models Employed

The simulated ST potentials were obtained from an accurate computer thorax model. The accuracy of the numerical method has been validated (20, 30, 31). The thorax model represents the anatomy of one individual, giving rise to error when the results are applied to other patients or population studies (32). In addition, the model did not consider all inhomogeneities; one weakness may be failure to consider the anisotropy of the heart muscle. Full-scale thorax models with anisotropic heart muscle have not yet been introduced, and this imperfection has an undetermined effect on thorax surface potentials. The anisotropy may further smooth the body surface potential distributions thus reducing the ability of the ECG to identify the injury source. Therefore, the use of isotropic heart muscle may not have a major effect on the conclusions of this study.

A number of studies have shown the effects of the constituents of the thorax to be important (15–18,33,34). Thus the simple solid angle analysis based on a uniformly conducting volume conductor may be suitable only for demonstrating the basic idea of the detection of the injury sources. To analyze the ability of the ECG leads to detect these sources, a more accurate model such as is used in this study is needed.

In this study, a subendocardial double-layer source model representing the potential difference of adjacent ischemic and normal myocardial cells was used. The electric strength of the double layer was considered homogeneous and the spatial properties were considered static throughout the exercise test. The model is idealized to the extent that some studies disagree with the notion that the source is located at the border. A volume source would provide a more accurate model (35). On the other hand, the results of studies that have examined the relationship between calculated potentials and those obtained on the epicardium of pig hearts support the hypothesis that the source is located at the border (5,12). Good correlation has also been observed between the potentials calculated by using the double-layer source model and the potentials on a homogeneous cylindrical tank model including an isolated canine heart (8) as well as an isolated rabbit heart (13). In addition, it has been shown that in exercise-induced transient subendocardial nontransmural ischemia, the depth of the ischemic region in the myocardium is small and the importance of the border zone is greater (2). Therefore, in simulations of precordial potentials the double-layer model may provide a valid representation of the sources arising during the ST-segment. A more detailed model of the source including the exact form of the ischemic regions (taking account of islands of surviving fibers, etc.) as well as membranous ionic currents would indeed increase the accuracy. However, the present knowledge of the changes in the myocardial syncytium during ischemia is limited, and the complicated changes in myocardial activation can only be realized by using cellular level simulations. In addition, the aim of this study was to evaluate the relationship between ST-segment parameters and the basic constituents of ischemic injury. This relationship might have been obscured by increasing the source accuracy and number of parameters. Furthermore, the generality of the source model would have been lost, since the structural details of the ischemic territories in each patient are bound to be different.
Conclusions

The aim of this computer model study was to determine the relationship between ST-segment parameters and the constituents of the ischemic injury, especially the supposed linear relationship between the area of the ischemic boundary and the ST/HR slope. The source model employed was based on the theoretical framework of the ST/HR slope introduced by Okin and Kligfield (9). In this study the effects of the torso as a volume conductor and the influence of multivessel disease on ST-segment response were introduced. Our computer simulations permit the conclusions discussed below.

Detection of the Presence of Ischemia

The simulation results supported the use of leads V4 and V5 to indicate ischemia when a criterion of at least 10 mV is employed. Use of specific criteria for other leads may improve the diagnosis.

Detection of the Extent and Location of Ischemia

Each ECG lead has a specific sensitivity in detection of the injury sources, providing different views of the injury. Especially in multivessel CAD, no lead exists that provides conclusive information regarding the complex sources. Thus, all the leads of the 12-lead ECG should be considered.

ST-segment deviation is affected by various factors, such as the area of the ischemic boundary, the metabolic depth of ischemia (i.e., injury source strength), and the ECG lead used. Thus, ST-segment deviation does not provide a method for diagnosing the extent or location of the myocardial injury.

The ST/HR slope has been suggested to provide a method that evaluates the solid angle of the ischemic lesion indicated by the ECG lead. However, the solid angle is only related to the area of the boundary between the healthy and ischemic myocardium for small injury sources. Especially in multivessel CAD, the total solid angle and the extent of the ischemic territory are not related. On the other hand, since lead V5 detects anterior, lateral, and inferior ischemias as ST-segment depressions, the ST/HR slope of lead V5 may indicate the extent of ischemia, providing that the ischemic lesion is situated in the regions mentioned above.

Linearity of the ST/HR Relation in Multivessel Coronary Artery Disease. We demonstrated that a linear ST/HR slope representing the entire ischemic part of the exercise test may be expected only in single-vessel CAD. In multivessel CAD, the spatial and temporal behavior of the injury sources will distort the linear ST/HR relation. Furthermore, the final linear segment of the ST/HR slope (which is selected as a clinical parameter) does not include all available information about the disease; therefore, the view of the ST/HR relation should be expanded. A more detailed analysis than one based on a linear regression model of the behavior of the ST/HR relation of the 12-lead ECG during the exercise test may provide information regarding extent of the injury, the number of diseased vessels, and the extent of the occlusions.

Limitations of the Study

Our results are based on a considerably more accurate description of the thorax than that which arises from a simple solid angle analysis. However, it should be stressed that the simulated ST deviation and ST/HR relations obtained in this study are based on a highly idealized situation and the nonlinear multivessel ST/HR slopes presented here are examples designed to demonstrate the behavior of the ST/HR slope. The nonlinearity of the slopes will appear in different forms and may be obscured by a number of factors. Clinical ST-segment deviation and HR-adjusted ST-segment include various factors not considered here, such as anatomic interpatient variation, pathophysiology of the myocardial artery occlusions and ischemia, HR variability induced by the exercise protocol and physiologic control systems, etc. In addition, the uncertain relationship between HR and metabolic depth of ischemia, as well as the inaccurate nature of the ischemic injury source, calls for further study.

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References


