ECG-based Estimation of Area at Risk in Acute Myocardial Infarction

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Abstract

We hypothesized that not only the location but also extent of myocardial ischemia (area at risk, AAR) during acute myocardial infarction could be estimated from the spatial distribution of ST-segment deviations in the ECG.

Standard 12-lead ECGs and SPECT images were obtained from 75 patients. Precordial ST-segment deviations were organized according to spatial orientation. An ST-profile was obtained: a semicircle of ST-deviations centered on the ST-injury vector. Spatial features of the profile were calculated, the R wave vector magnitude was obtained, and an automated method of patient separation into culprit artery groups was developed. A linear regression model between optimal features and AAR yielded: $r = 0.64$ ($p < 0.01$).

AAR extent can be estimated from the magnitude of ST-deviations and R wave. The spatial distribution of ST deviations is indicative only of the location of AAR, not of extent.

1. Introduction

Myocardial infarction is a major global cause of death and disability. In acute myocardial infarction (AMI), the infarct size is known to be an important predictor of survival and congestive heart failure [1], and the most significant predictor of final infarct size is the extent of ischemic myocardium [2] referred to as area at risk (AAR). The prognosis of many AMI patients is poor despite successful reperfusion treatment, and the development of new treatments for these patients will benefit from better risk stratification in the acute phase.

Several methods exist for estimation of AAR or final infarct size. These include myocardial perfusion imaging by single photon emission computed tomography (SPECT) and measurement of biomarkers. However, these techniques produce results only after vital triage decisions have already been made and SPECT imaging is costly. Electrocardiograms (ECG) are however routinely recorded in early triage. As the ECG is inexpensive, non-invasive and available from the onset of care, attempts have been made to utilize it to estimate AAR [2-4].

Myocardial ischemia is known to be associated with an electric injury current, giving rise to measurable changes in the ECG, the most prominent being deviations of the ST-segment. *Aldrich et al.* presented an ECG scoring system predictive of final infarct size [3]. However, in a later study this score did not correlate well with SPECT estimated AAR ($r = 0.14$) [4]. Taking a different approach, *Strauss et al.* and *Andersen et al.* both employed a method based on the vectorcardiogram (VCG) [2,4].

In the VCG, the electric activity of the heart is described by a fixed dipole vector with direction and magnitude. *Hurst* considered the implications of applying vectorcardiography to describe the injury current [5]. Interpreting pathologic ST-segment deviations as projections of injury current oriented outwards from ischemic myocardium, the spatial direction of the resulting ST injury vector was hypothesized to be towards the location of transmural myocardial ischemia [5].

Dower et al. developed a set of leads for deriving the 12 lead ECG from the three VCG leads for an average human torso [6]. Reasoning that increased AAR is associated with stronger injury current, both *Strauss et al.* and *Andersen et al.* derived the ST injury vector from the 12 lead ECG by inverse Dower transform. *Strauss et al.* found a correlation between ST vector magnitude and SPECT estimated AAR ($r = 0.68$) for 32 patients, while *Andersen et al.* using the same approach for 75 patients found much lower correlation ($r = 0.29$).

In these studies the ST injury vector method was applied based on an assumption that the electric activity during AMI is well described by the dipole model. However, we reasoned that if each area of ischemic myocardium gives rise to an outwardly directed injury current, then these injury currents may be represented by a number of differently oriented and distributed dipoles. Consequently, we hypothesized that the non-dipolar components of the injury current result in changes in the spatial distribution of ST-segment deviations, meaning that a larger AAR would be associated with deviations over a greater range of directions. We applied spatial ECG analysis to investigate this hypothesis.

2. Methods and materials

The study population was a total of 75 retrospectively selected AMI patients treated with acute angioplasty. All had occlusive single-vessel disease with TIMI flow 0/1 determined by coronary angiography as well as ST-segment deviations of at least 0.1mV in at least two contiguous leads (if V1-V3: 0.2mV in men, 0.15mV in women). Patients with signs of left bundle branch block, prior infarction or left ventricular hypertrophy were excluded. Patients were grouped by culprit artery: Left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) (30 LAD, 17 LCX, 28 RCA).

ECGs of 10s duration were recorded immediately prior to coronary intervention by qualified professionals using the Mason-Likar electrode configuration.

Each patient received an intravenous injection of $700 \pm 10\%$ MBq^{99m}Tc-Sestamibi prior to intervention. Myocardial perfusion imaging by SPECT was performed within two hours of injection. Images were analyzed independently by two physicians who were specialists in nuclear cardiology, and AAR was assessed by consensus.

The ECG and SPECT data used were the same as those used by *Andersen et al.* [4]. However, SPECT based estimates of AAR were reevaluated for this study.

To compare results with manual clinical estimates of AAR, the ECG data were presented to three experienced cardiologists at Aarhus University Hospital, Skejby.

2.1. The ST Profile method

Median beats were formed and ST segment deviations were measured in all leads at the J-point + 40ms.

A 360º visualization of precordial ST-segment deviations was created. Lead orientations were derived from the Dower lead vectors and projected into the horizontal plane. In accordance with vectorcardiography, hypothetical inverted precordial leads were also included. These were oriented in the opposite directions and were assigned the negative of the measured ST-segment deviations. The deviations were interpolated to provide a curve for analysis. The direction of the ST injury vector in the horizontal plane was derived by inverse Dower transform, and a 180º segment of the curve centered on this direction was extracted. This extracted interval was referred to as the *ST Profile* see Figure 1. Several features based on the stated hypothesis were calculated.

2.2. Features

ST Profile Width: In accordance with our hypothesis, the width of the profile was expected to increase with greater AAR. To measure profile width, an equation from probability theory was employed. Variance (or second central moment) is a measure of the width of the probability distribution of a random variable.

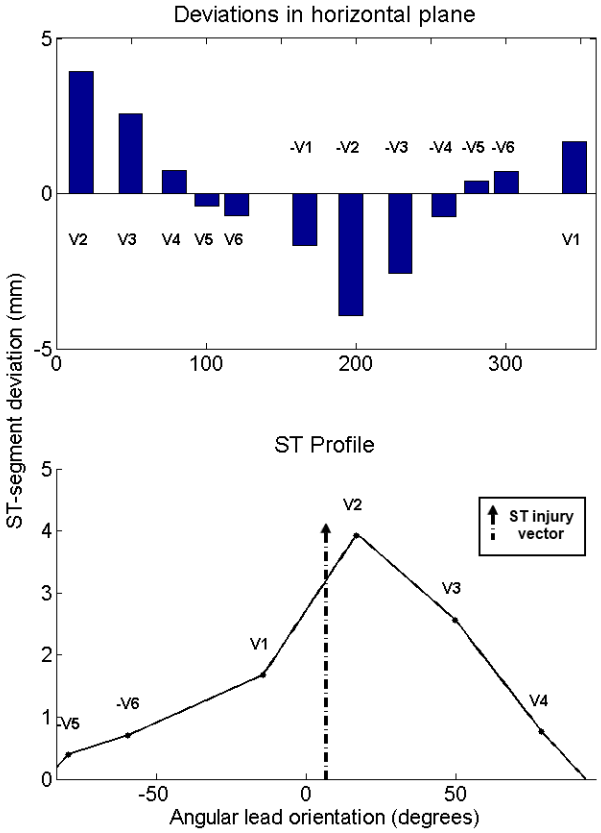

Figure 1. The ST Profile method for an LAD patient. Top: A 360º view of the normal and inverted precordial ST-segment deviations in the horizontal plane (0º: Frontal direction). Bottom: A 180º interpolated profile centered on the ST-injury vector.

The ST profile function $d(\theta)$ was divided by the sum of itself, as variance is defined for probability distributions with sum equal to 1. The first moment about zero was calculated by:

$$\mu_1' = \sum \theta_i d(\theta_i)$$

Here, θ_i is the i'th angular value. The second central moment was calculated by:

$$\mu_2 = \sum (\theta_i - \mu_1')^2 d(\theta) = \sigma^2$$

ST Profile Flatness: The flatness of the profile was also expected to increase with AAR. Similarly as for width, an equation from probability theory was used. Kurtosis is the flatness of a probability distribution. It is based on the fourth central moment and was calculated by:

$$kurtosis = \frac{\sum(\theta_i - \mu_1')^4 d(\theta)}{(\sum(\theta_i - \mu_1')^2 d(\theta))^2}$$

ST Profile Sum: Following our hypothesis, greater AAR should result in a greater spatial distribution of ST-segment deviations as well as increased magnitude of injury current. This would result in a greater area under

the profile. This area was calculated as the sum of positive deflections.

ST Profile Amplitude: The amplitude of the profile was also calculated as the maximal positive deflection.

R Vector Magnitude: Due to the changes in electric activity in ischemic myocardium, it might be expected that net electric activity be reduced during the ventricular depolarization underlying the R wave. To quantify this, the maximal magnitude of the dipole vector during the QRS complex was calculated.

2.3. Grouping by culprit artery

The location of ischemia and AAR depends on the culprit artery, and it is possible to locate the ischemic area from the direction of the ST injury vector [4]. We attempted automatic separation of patients into two culprit artery groups: LAD and non-LAD. In order to separate these groups a plane intersecting the origin was defined through an optimization process. Patients were grouped by determining on which side of this plane the ST injury vector was located.

2.4. Modeling and validation

Predictive models were created by linear regression. A full model was created by selecting the feature with the strongest correlation with AAR and including features that increased the adjusted coefficient of correlation. A simplified model was also created for manual use. Models were validated by k-fold cross validation (fold size: 5) in order to estimate the expected performance for independent data. For comparison of correlations the Kullback test was used. All p-values less than 0.01 were considered significant.

3. Results

Table 1. Correlations between features and AAR.

Feature	r	p
Width	-0.14	0.22
Flatness	0.03	0.77
Sum	0.42	<0.01
Amplitude	0.40	<0.01
Sum/|R|	0.48	<0.01
Log_e(Sum/|R|)	0.57	<0.01
|R|	-0.41	<0.01

The correlations between features and AAR are shown in Table 1. Significant correlation was found for profile sum and amplitude, but not for width and flatness. Sum and amplitude were strongly intercorrelated ($r = 0.977$). Normalization of the ST profile sum by the magnitude of the VCG at R peak as well as transformation by the natural logarithm improved the correlation between profile sum and AAR. The R vector magnitude was also significantly negatively correlated to AAR.

The plane obtained to separate culprit artery groups by ST injury vector orientation resulted in perfect separation between the LAD and non-LAD groups.

The full model included the log transformed normalized profile sum, the R vector magnitude and automatic culprit artery grouping:

$$AAR = 23 + 5.6 \times log_e\left(\frac{ST_{sum}}{|R|}\right) - 5.7 \times |R| + 5.24 \times L$$

Here $L = 1$ for LAD patients and $L = 0$ for non-LAD. The simplified model for manual use included ST amplitude normalized by maximal R wave amplitude:

$$AAR_{simple} = 47.6 + 8.7 \times log_e\left(\frac{ST_{amp}}{|R_{amp}|}\right)$$

Results were compared with earlier proposed methods. The Aldrich score was implemented as described by *Bacharova et al.* [7]. For comparison with *Strauss et al.* [2] and *Andersen et al.* [4], the ST injury vector magnitude was calculated and a linear regression model was validated by k-fold cross validation. The results obtained for our models, earlier methods and the three clinical estimates are shown in Table 2.

Table 2. Results for each method. Shown: correlation (r), coefficient of determination (r^2) and root mean squared error (RMSE in percentage of left ventricle).[1]: RMSE obtained by k-fold cross validation.

Method	r	r^2	RMSE
Full model	0.64	0.41	10.86[1]
Simple model	0.55	0.31	11.56[1]
$\|ST_{inj}\|$	0.27	0.08	13.19[1]
Aldrich score	0.06	0.00	20.45
Clinician 1	0.48	0.23	15.20
Clinician 2	0.44	0.19	13.82
Clinician 3	0.38	0.14	15.25

For the Aldrich score, eight patients did not meet the inclusion criteria. K-fold cross validation of our model provided more accurate estimates of AAR than was obtained with the Aldrich score.

The descriptiveness of our full model was greater than the ST injury vector magnitude for these data. *Strauss et al.* however, reported a spearman correlation between ST injury vector magnitude and SPECT estimated AAR of $r = 68$ [2]. This was greater than the correlation for the ST injury vector magnitude for our data. The two study populations were however quite different. In the study by *Strauss et al.*, ECGs were recorded during artificial occlusion of a coronary artery for 32 patients, and ST-segment deviations were measured as the difference between the occluded and non-occluded ECG. The data used in our study were recorded for 75 patients presenting

with acutely occurring myocardial ischemia. As such, time dependent developments of ST-segment deviations were likely more influential.

4. Discussion

For the ST Profile features a very strong intercorrelation between sum and amplitude was found, while width and flatness did not show significant correlation with AAR. This suggests that, while the magnitude of deviations increases with AAR, the distribution of deviations adds little additional information. This did not support the initial hypothesis that greater AAR would increase the spatial distribution of ST-segment deviations. It also suggests that the extent of the ischemic area does not affect the ability of the dipole model to describe the electric activity recorded in the ST-segment.

One possible physiological explanation for this observation could be the higher conductivity of blood relative to myocardium. This may in effect act as a short circuiting of the ventricle across the ventricular cavity, causing injury current dipoles to approximately originate at the center of the ventricular cavity. The signal arising from multiple dipoles originating in the same location would be equivalent to the signal from the single dipole resulting from a superposition of these dipoles.

ECG based estimation of AAR is of course highly dependent upon a reliable and accurate reference measure for validation. In this and several earlier studies, SPECT imaging was used, which means that results were ultimately limited by the accuracy of SPECT estimates. *Åkesson et al.* investigated inter-operator variability in quantitative analysis of reversible perfusion defects by SPECT [8]. Differences in estimates of ischemic extent greater than 10%LV were observed between operators selected from the same department applying identical procedures. Greater variability between clinical sites may be expected. Thus, it appears that the accuracy obtainable is constrained by the accuracy of SPECT estimates. Future improvements in imaging techniques may therefore also improve ECG based techniques.

In a clinical context, the results of this study indicate that the distribution of leads or number of leads with ST-segment deviation should not be interpreted to provide information about AAR additional to that of the general magnitude of deviations. Our simplified model is well suited to manual paper-based application with only a ruler and calculator. While this model did not produce estimates as accurate as the full model, the results were comparable. It is important to note that our models were validated by k-fold cross validation and not a test with independent data. However, this validation indicated that estimates obtained with the simplified model were more accurate than the Aldrich score.

5. Conclusion

A method for analysis of ST-segment deviations in the horizontal plane was developed. Models for estimation of AAR during AMI based on spatial analysis of the ECG were developed. The results of this study indicate that the magnitude of ST-segment deviations increases with greater AAR, but that the spatial distribution of deviations is not related to AAR. Results also indicate that a greater AAR is associated with decreased R wave energy. It was possible to perfectly separate LAD and non-LAD patients by automatic analysis of ST injury vector orientation. No evidence was found for the accuracy of the ST injury vector model being affected by AAR.

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