A dynamic model forecasting myocardial infarct size before, during, and after reperfusion therapy: an ASSENT-2 ECG/VCG substudy

Per Johanson¹,²*, Yuling Fu³, Shaun G. Goodman⁴, Mikael Dellborg¹, Paul W. Armstrong³, Mitchell W. Krucoff², Lars Wallentin⁵, and Galen S. Wagner²

¹Division of Cardiology, Sahlgrenska University Hospital/O¨stra, SE-41685 Göteborg, Sweden; ²Duke University Medical Center, Durham, NC, USA; ³University of Alberta, Edmonton, Canada; ⁴Canadian Heart Research Center, and Terrence Donnelly Heart Centre, St Michael’s Hospital, University of Toronto, Canada; and ⁵Thoraxcenter, Akademiska Hospital, Uppsala, Sweden

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Aims Serial forecasts of final myocardial infarct (MI) size during fibrinolytic treatment (Rx) of ST-elevation MI would allow the identification of high-risk patients with a predicted major loss of viable myocardium, at a point when treatment may still be modified. We investigated a model for such forecasting, using time and the ECG.

Methods and results We collected 234 patients with ST-elevation MI, without signs of previous MI, bundle branch block, or hypertrophy. MI size was determined by the Selvester score and was ‘forecasted’ at: admission with patients stratified by delay time and an ECG acuteness score into three groups (EARLY, DISCORDANT, and LATE); 90 min after Rx by ≥70% ST-recovery or not and occurrence of “reperfusion peaks”; 4 h after Rx by ST re-elevations. EARLY patients had smaller final infarct sizes than LATE (9.4 vs. 20%, \( P = 0.01 \)). EARLY patients with ≥70% ST-recovery without a reperfusion peak had smaller infarct sizes than those with (3.1 vs. 12.5%, \( P = 0.001 \)). EARLY patients without ST re-elevations had smaller infarct sizes (1.5%) than those with some (9%) or many re-elevations (12%), \( P < 0.001 \).

Conclusion Final infarct size can be forecasted using delay time and serial ECGs. Serially updated forecasts seem especially important when both clock-time and initial ECG-sigs indicate earliness.

Introduction

Treatment of ST-elevation myocardial infarction (STEMI) aims at early myocardial reperfusion in order to salvage myocardium, reduce final infarct size and, consequently, to achieve improved clinical outcome.

Serial forecasts of ‘salvagability’ and final infarct size before, during, and after reperfusion treatment of STEMI would allow the identification of (i) high-risk patients with a predicted major loss of viable myocardium at a stage when treatment may still be modified and (ii) low-risk patients with predictions of small infarcts and good outcome after primary reperfusion therapy. This paper examines a model for such serial forecasting, using evolving time and ECG-analyses to stratify patients with STEMI.

The amount of myocardium at risk for infarction can be assessed by ST-segment analyses from the admission ECG.¹ ² This first ECG can also be used to estimate the ‘acuteness’ of the infarction process³ complementery to information from symptom delay.⁴ Treatment efficacy, i.e. speed and quality of restoration of epicardial flow⁵ ⁶ and myocardial perfusion⁷ ⁸ can be assessed by ST-segment recovery analyses. Rapid, high-grade, and stable ST-recovery has consistently been associated with better clinical outcome.¹⁰ ¹³ This association is likely secondary to the fact that faster restoration of myocardial perfusion results in greater myocardial salvage and smaller infarct size.¹⁴ Recent studies have shown that early and complete ST-recovery is indicative of smaller infarct size.¹⁵ ¹⁶

We hypothesized that combinations of clock-time and previously evaluated ECG variables could be useful for serially updated forecasts of final infarct size and that these forecasts would change with ECG signs of successful/unsuccessful reperfusion treatment.

Methods

Patients

The present study was conducted as a substudy of the second Assessment of Safety and Efficacy of a New Thrombolytic (ASSENT 2)
trial. The ASSENT 2 trial was a multicenter study comparing tenecteplase with standard, front-loaded alteplase. Inclusion and exclusion criteria for these patients with ST-elevation infarction within 6 h of symptoms were detailed in the report of the main study. For inclusion in the present substudy, availability of an admission ECG, either a discharge ECG or, if missing, a 24–36 h ECG, and continuous ST-monitoring data were required. Out of the 374 patients from the vectorcardiographic (VCG) ST-monitoring substudy of the ASSENT 2, 303 fulfilled these criteria.

Quantitative analyses of serial ECGs
Serial ECGs were read by readers at the ECG Core Laboratories (Canadian VIGOUR Centre, University of Alberta, Edmonton and Canadian Heart Research Centre, Toronto) without knowledge of outcomes.

Admission ECG
The amount of ST-segment deviation (from the reference level in the PR segment) was measured manually using a hand-held caliper at J + 20 ms. On the basis of the lead with the maximal ST-deviation, patients were divided into anterior or inferior infarct location. Patients with maximal ST-elevation in leads V1–V3 were classified as anterior, whereas those with maximal ST-elevation in II, aVF, or III (or ST-depression in V1–V3) as inferior location. ST-deviation in the admission ECG was summated according to the Aldrich ST-score to estimate the area jeopardized for infarction. The Anderson–Wilkins (AW) acuteness score was also calculated from the admission ECG. This score ranges from 1.0 (least acute) to 4.0 (most acute) and takes QRs-, ST-, and T-measurements into consideration for judgment of how early during the infarct process the ECG was recorded.

Pre-discharge ECG
Final infarct size was defined by the Selvester QRS score either from the pre-discharge ECG or, if such an ECG was not available, from the 24–36 h ECG. Selvester scoring of the QRS-complex has previously been detailed. Briefly, this QRS score is based on the consideration of 50 criteria, producing a maximum of 31 points, each of which representing ~3% infarction of the left ventricle.

ST-monitoring
Patients were monitored for 24 h after admission with high-fidelity digital continuous ST-monitoring, using the MIDA system for continuous VCG (Ortvis Medical AB, Täby, Sweden). By this system, ST-vectormagnitude (ST-VM) is calculated from the orthogonal leads X, Y, and Z, according to the formula: ST-VM = \sqrt{(Xi^2 + Yi^2 + Zi^2)} and represents the total, spatial ST-segment deviation from the baseline. Xi, Yi, and Zi are the magnitudes of ST-deviation in the three leads. ST-VM is presented online on a computer screen as a trend curve (Figure 1). ST-segment changes were measured 20 ms after the J-point.

Trend-curve analysis
Times to 50 and 70% ST-segment recovery from maximal ST-elevation as well as %ST-recovery at 90 min after treatment were registered. Initial ST-elevation on the admission ECG was derived from leads V2, aVF, and I into an ST-VM data point and included in the calculation of ST-recovery at 90 min.

As in previous VCG-studies on recurrent ST-elevations, during the first 4 h, an increase in ST-VM from 1 min to the other exceeding 25 μV for ≥2 min was counted as an ST-event. During such events, the total area under the ischemia curve (AUC) was summed (μV × min).

Exacerbation of ST-segment elevation at the time of reperfusion is proposed as a sign of poor outcome, indicating a reperfusion syndrome. We prospectively defined the occurrence of a marked (>80 μV) and rapidly evolving (<5 min) exacerbation of ST-VM, if it occurred prior to ≥50% ST-recovery and within 90 min from onset of therapy, as a reperfusion peak. All analyses were made by two blinded and independent observers at the Ischemia Core Lab, Sahlgrenska University Hospital/Ostra, Göteborg.

Modelling of the serial forecast method
Three serial forecasts were done at admission, 90 min, and 4 h after treatment (Figure 2). (i) The first forecast of final infarct size was based on estimating the acuteness of the AMI by combining the patient-recalled symptom onset to hospital presentation delay by historical clock-time and the AW acuteness score from the admission ECG. As previously described, these two variables were dichotomized using a <2 h cut-off to define earliness by time and a ≥3 AW-score cut-off to define earliness by the ECG. Patients were divided into three groups: those that were concordantly early by both variables (EARLY), those that were concordantly late (LATE), and those where the two variables were discordant (DISCORDANT). (ii) In the second forecast, at 90 min after treatment, the previous three groups were subdivided by presence or absence of complete (≥70%) ST-recovery and by occurrence of a reperfusion peak in the continuous ST-monitoring. ST-recovery was calculated from maximal ST-elevation. (iii) In the third forecast, at 4 h after treatment, the three groups were subdivided by recurrence of ST-elevations only, irrespective of ST-recovery. Recurrent ST-elevations were quantified by their AUC, which was used to form the three subgroups: (1) None, (2) Yes, but smaller than the median AUC, and (3) Yes, greater than or equal to the median AUC.

Statistical analysis
Statistics were calculated with the SPSS 11.5 (SPSS Inc. Chicago, IL, USA). Continuous variables are reported as means or medians and one-way ANOVA or the Kruskal-Wallis test was used to compare the differences among groups. For categorical variables, the data were summarized in percentages and the \( \chi^2 \) test was used to assess group differences. Categorical variables with more than two categories were analysed with the \( \chi^2 \) test for trend. All tests were two sided, \( P < 0.05 \) was considered significant.

Model development
Three models were developed sequentially in our study (Table 3), incorporating information collected on admission, at 90 min, and 4 h. The following variables were included in each of the predicting infarct size models (i) on admission: baseline patient demographics data (Table 1), presenting characteristics, Aldrich score and
acuteness score. (ii) At 90 min: in addition to the baseline demographics data, presenting characteristics, Aldrich score and acuteness score, the variables complete ST-recovery at 90 min, and occurrence of a reperfusion peak were added into the model. (iii) At 4 h: occurrence of ST re-elevation by 4 h was added into the model in addition to the variables included in the 90 min model. Multiple logistic regression procedures based on the stepwise, backward variable selection method were used to develop these models. The models were evaluated on the basis of the discriminatory capacity (i.e. c-statistic) and the linearity assumption was tested using the Box-Tidwell test.

Results

Patients

Of the included 303 patients with VCG and ECG data, 23 were excluded due to bundle branch or fascicular block, 21 due to ECG signs of hypertrophy, 13 due to signs of previous infarction, and 12 since infarct location could not be classified as either inferior or anterior; leaving 234 patients in the analysis. Patient demographics are shown in Table 1. Overall 30 day mortality was 1.3%.

Patient delay was assessed by historical time and AW acuteness score. One-hundred and seventeen patients (50%) had a delay time 

Second forecasting of final infarct size: at 90 min

In the 90 min analysis, complete ST-recovery (≥70%) when compared with non-complete (<70%) recovery, did not influence the final infarct size in any of the three groups. Median infarct size was 9.4% in both EARLY and DISCORDANT patients and 20% in LATE patients, in both of the ST-recovery groups. Similarly, no influence on infarct size was found in either of the group when using 50% ST-recovery as cut-off, instead. In fact, the results were identical.

However, in the EARLY group, occurrence of a reperfusion peak prior to ST-recovery, i.e. a marked and rapidly evolving worsening of ST-elevation after onset of treatment, was associated with significantly larger infarcts (12.5 vs. 3.1% of the left ventricle, P = 0.001) among patients with ≥70% ST-recovery (Figure 4). In the DISCORDANT and LATE groups, the admission forecasts of 'medium' and 'large' final median infarct size, respectively, were not changed significantly by either presence of a reperfusion peak or ST-recovery at 90 min. Again, the area of initially jeopardized myocardium (Aldrich score) did not vary significantly between the groups (Figure 4).

Third forecasting of final infarct size: at 4 h

Figure 5 shows median infarct size in the three groups, subdivided by occurrence of ST-re-elevations, expressed as AUC. In the EARLY group, absence of ST re-elevation resulted in a median final infarct size of only 1.6% of the left ventricle, when compared with 9.4 and 12.5% for those with ST-re-elevations below and above median ischemic AUC (516 μV min), respectively (P < 0.001). In the DISCORDANT group, there was a non-significant trend towards smaller infarct sizes among patients without ST re-elevation (6.2 vs. 9.4 vs. 9.4%, P = 0.3), whereas in the LATE group, the initial admission forecast of a large final infarct size was unchanged by absence or presence of recurrent ST-elevation.

Multivariable analysis

The three sequential multivariable analyses are presented in Table 3, showing that both the Aldrich score (jeopardized myocardium) and the Acuteness score, yield independent information on final infarct size at all of the three time points. Occurrence of a reperfusion peak within 90 min and ST re-elevation within 4 h add further independent information. The C-indices for these three models are 0.78 at admission, 0.80 at 90 min, and 0.80 at 4 h, respectively.

Discussion

The main finding of this study is that serial analyses of different components of the ECG waveform and historical clock-time can be combined to improve and update predictive information on infarct size before, during, and after fibrinolytic treatment of an STEMI. The sequential multivariable analyses show that initially collected ECG data, estimating the amount of jeopardized myocardium and the acuteness of the myocardial infarction (MI), carry independent information on outcome, superior to baseline data, and other presenting characteristics. Further, continuous, collection of ECG data during the first 4 h adds further independent information. Indeed, such combined analyses of pre-
treatment data indicating the acuteness of an infarct, and data indicating rapidity, quality, and stability of restoration of myocardial perfusion during and after treatment have not previously been reported.

First forecasting of infarct size

We have demonstrated that a combined analysis of ECG and time variables clinically available at first contact might be of use for identifying patients who are more likely to benefit from fibrinolytic reperfusion therapy and possibly those who will benefit less from such therapy. In patients with one or both of these variables indicating earliness, final infarct size was significantly smaller, and 50% of the final infarct size that was found in patients with both variables indicating lateness. These observations are consistent with previous findings. Historical timing of the acuteness of an AMI, i.e. the patient’s description time-delay from symptom onset to hospital presentation and initiation of therapy, has shown that early reperfusion therapy resulted in smaller final infarct size, irrespective of how much myocardium that was initially jeopardized.24 The model for using the AW acuteness score from the admission ECG together with historical timing, has been explored and shown to refine the estimation of acuteness of an AMI.4 In the current population, however, median delay times did not differ significantly over the quartiles of infarct size (Table 2). Furthermore, our findings in the DISCORDANT group indicate that when delay time and the acuteness score point in different directions, the acuteness score probably gives a better estimate of the earliness of an AMI.

Second forecasting of infarct size

Rapid and high-grade ST-segment resolution following an acute MI has been associated with better left ventricular function,10,25,26 smaller final infarct size as measured by enzymes,10,15 and Selvester QRS-scoring of the pre-discharge ECG,15 and with greater myocardial salvage, measured by nuclear imaging.16 Rapid and high-grade ST-segment resolution has consistently been shown to be useful for early identification of patients at low- or high risk for subsequent morbidity and mortality.10,13,27 We expected that patients who were early by both historical time and AW-score and had a high-grade early ST-recovery would have small final infarct sizes. Contrary to these expectations, complete ST-recovery within 90 min as opposed to non-complete ST-recovery, was not by itself associated with smaller final infarct sizes in any of the three groups. Similarly, smaller infarct size was not preceded by shorter median times to 50 or 70% ST-recovery. This potential inconsistency might, however, be explained by the fashion, in which ST-segment resolution is calculated during continuous ST-monitoring: the reference value is continuously updated, using the preceding peak value for the calculations of ST-resolution at a certain time. When considering

<table>
<thead>
<tr>
<th>Table 1 Demographics</th>
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<tr>
<td><strong>All</strong></td>
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<tr>
<td><strong>EARLY</strong></td>
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<tr>
<td><strong>DISCORDANT</strong></td>
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<tr>
<td><strong>LATE</strong></td>
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<tr>
<td><strong>P-value</strong></td>
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<tr>
<td>n</td>
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<tr>
<td>Age (mean ± SD)</td>
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<tr>
<td>Female sex (%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
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<tr>
<td>Anterior MI (%)</td>
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<tr>
<td>Ever smoked (%)</td>
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<tr>
<td>Previous MI (%)</td>
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<tr>
<td>Previous PCI (%)</td>
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<tr>
<td>Previous CAGB (%)</td>
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SD, standard deviation; PCI, percutaneous coronary intervention; CAGB, coronary artery bypass grafting.

<table>
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<tr>
<th>Table 2 Individual distributions of the investigated time and ECG variables over final infarct size in quartiles</th>
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<tr>
<td>Final infarct size (% of LV)</td>
</tr>
<tr>
<td>0–3.1</td>
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<tr>
<td>n</td>
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<tr>
<td>Jeopardized myocardium by Aldrich score (% of LV)</td>
</tr>
<tr>
<td>12.3 (11.4–16.8)</td>
</tr>
<tr>
<td>Delay time (h)</td>
</tr>
<tr>
<td>2.0 (0.8–3.0)</td>
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<tr>
<td>Acuteness score</td>
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<tr>
<td>3.3 (3.0–3.7)</td>
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<tr>
<td>Percent ST-recovery at 90 min</td>
</tr>
<tr>
<td>56 (29–75)</td>
</tr>
<tr>
<td>Time to 50% ST-recovery (min)</td>
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<tr>
<td>44 (12–153)</td>
</tr>
<tr>
<td>Time to 70% ST-recovery (min)</td>
</tr>
<tr>
<td>168 (60–1400)</td>
</tr>
<tr>
<td>Occurrence of reperfusion peak (%)</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>Total area, recurrent ischemia (µV min)</td>
</tr>
<tr>
<td>94 (3–577)</td>
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</tbody>
</table>

Values are presented as medians (25th–75th percentiles). LV, left ventricle.
the occurrence of a significant worsening of ST-elevation, preceding ST resolution, here defined as a reperfusion peak, a group of patients with very small final infarct sizes could be identified. Absence of such a reperfusion peak was significantly associated with very small final infarct sizes among the EARLY patients with complete ST-recovery.

These findings are supported by previous reports. Additional ST-elevation at the time for the restitution of coronary flow to an infarct related artery has been shown in 27–50% of cases, and has, in most previous studies, been associated with unfavourable outcome such as reduced microcirculation, large infarct size, or impaired left ventricular function. In our study, angiographic measurements of coronary flow to correlate with the timing of the occurrence of a reperfusion peak were not available. However, the definition used has previously been found to correlate very well with angiographic reflow in patients with STEMI treated by either fibrinolytics or angioplasty.

### Third forecasting of infarct size

ST-segment re-elevations either during the first hours of fibrinolytic treatment of an STEMI or later during the first 24 h have consistently been associated with worse outcome measured as morbidity and mortality. Two previous studies address the possible relationship between ST re-elevations and infarct size. In these reports, patients with ST re-elevations had larger infarct sizes as measured by enzyme levels. When compared with the predictive information from mere ST-segment resolution at a certain time-point, ST-dynamics beyond this have been shown to yield further predictive information. In a previous study, we found that early ST-segment resolution did not contribute to the information on TIMI flow or persistence of thrombi in the culprit coronary artery 4–7 days after the acute event, whereas ST re-elevations during the first 24 h did.

Our expectations of smaller final infarct sizes in patients without ST re-elevations were confirmed, at least in the EARLY group. Patients with 'some' and 'more' re-elevations had a six- and eight-fold increase in final infarct size, respectively, when compared with those with no re-elevation.

### Clinical implications

Our findings suggest that the impact of thrombolytic therapy on final infarct size in patients with STEMI may be non-invasively forecasted and, at least in the EARLY patients, serially updated following the first ECG. The model could, therefore, be clinically valuable especially for patients who are early by both the ECG acuteness score and the delay time. In the present study, these patients had smaller final infarct sizes but were also the only ones who had significant changes in the subsequent forecasts on the basis of ECG dynamics. Their initial forecast of a 'small' infarct size, changed to either 'very small' in the subgroups with ECG signs indicating efficient reperfusion therapy or 'medium' in the subgroups without such signs. As for the LATE patients in this small study, it might actually be
questioned whether fibrinolytic treatment resulted in any gain at all, even if the groups are too small to conduct any meaningful mortality comparisons. The amount of initially jeopardized myocardium equalled the amount of finally infarcted myocardium in all subgroups of these patients, irrespective of subsequent ECG dynamics. Their initial forecast of a ‘large’ infarct size thus remained unchanged.

Combinations of bioelectrical markers such as the ones used in our model and biochemical markers could also be of further value. However, our methods, used both for assessing information from the admission ECG and for continuous assessments of ECG dynamics thereafter, are not routinely employed in clinical practice. Indeed, both the different scoring systems of static ECGs and the information from continuous ST-monitoring are generally employed in a research setting. Nevertheless, in an era of evolving digitized ECG analysis methods, automated systems for such scoring will be available in the near future. Furthermore, ischemia monitoring by continuous ST-monitoring is gaining favour both in research applications and as real time bedside monitors.

We believe this report provides novel information based on monitoring tools which can be routinely employed in the treatment of STEMI patients and may be combined for increased predictive value and for clinical decision making. However, these first findings require additional verification before recommending general use in STEMI risk stratification.
Limitations

Although the Selvester QRS score is well validated for the estimations of infarct size, the sole use of the ECG for infarct size definition is a limitation of this study. Moreover, this score probably yields a relatively wide variation in its correlation to anatomical infarct size and should, therefore, be considered as an estimate, not an absolute measurement of infarct size. As in many substudies, questions on representability of our population should be raised. The data loss due to lack of follow-up ECGs and the extensive exclusion criteria used for enabling the calculations of Selvester and AW acuteness scores have resulted in a study population with very low 30 day mortality when compared with the mortality in the main trial. The extensive exclusion criteria have also resulted in comparisons between rather small groups. It would, for instance, at the 4 h forecast, have been desirable to include the subdivider used at 90 min (complete vs. non-complete ST-recovery), but the patient groups would then have become far too small.

Finally, the consideration of reperfusion peaks in this particular analysis was a post hoc decision even if this variable actually was prospectively defined when first deciding which variables to collect when designing the original ST-monitoring substudy.

Acknowledgements

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Appendix 1

Acuteness score ECG classification

<table>
<thead>
<tr>
<th>Phase</th>
<th>ST†</th>
<th>T wave</th>
<th>Abn. Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A (4 points)</td>
<td>+ or -</td>
<td>TT</td>
<td>-</td>
</tr>
<tr>
<td>1B (3 points)</td>
<td>+</td>
<td>PT</td>
<td>-</td>
</tr>
<tr>
<td>2A (2 points)</td>
<td>+ or -</td>
<td>TT</td>
<td>+</td>
</tr>
<tr>
<td>2B (1 point)</td>
<td>+</td>
<td>PT</td>
<td>+</td>
</tr>
<tr>
<td>3 (0 points)</td>
<td>+</td>
<td>EN or FT</td>
<td>+</td>
</tr>
<tr>
<td>4 (0 points)</td>
<td>+</td>
<td>MN</td>
<td>+</td>
</tr>
<tr>
<td>Unknown (0 points)</td>
<td>+</td>
<td>EN, FT or MN</td>
<td>-</td>
</tr>
</tbody>
</table>

Each ECG lead is classified according to a scoring of different ECG-phases (Anderson et al. J of Electrocardiologe 1993, Vol. 25). For abbreviations, see panel below.

Appendix 2

The Selvester scoring system

- **ST** > 0.1 mV at 1 point
- **T wave changes**
  - Tall T waves (TT)
    - >0.1 mV in V2-V4
    - >0.75 mV in V5
    - >0.5 mV in V1, V6, I, II, aVf
    - >0.25 mV in aVL, III
  - Positive T waves (PT)
    - >0.5 mV but not TT
  - Flat T waves (FT)
    - <0.05 mV, either positive or negative
  - End of T negative (EN)
    - initial ≤50% of T positive but terminal <50% negative by ≤0.05 mV
  - Middle of T negative (MN)
    - ≤50% of T negative by ≤0.05 mV
  - Abnormal Q waves
    - according to the Selvester QRS scoring system

Acuteness score calculation

The Acuteness Score (AS) is calculated by dividing the sum of points by the number of leads involved (aVR not included)

\[ \text{PAS} = \frac{4(\text{no. of leads 1A}) + 3(\text{no. of leads 1B}) + 2(\text{no. of leads 2A}) + 1(\text{no. of leads 2B})}{\text{no. of leads with 1A, 1B, 2A, or 2B}} \]

Appendix 2

The Selvester scoring system
References