Clinical research

Admission Troponin T and measurement of ST-segment resolution at 60 min improve early risk stratification in ST-elevation myocardial infarction

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Received 29 April 2003; received in revised form 19 September 2003; accepted 23 October 2003

This paper was guest edited by Prof. Harvey White, Department of Cardiology, Green Lane Hospital, New Zealand

Introduction

During many years risk stratification of patients with ST-elevation myocardial infarction (STEMI) was based on variables from the patients’ history, physical examination and ECG on admission. Variables such as age, blood pressure, heart rate, Killip class and infarct location have been identified as important predictors of outcome.1 In recent years additional variables for early risk stratification in STEMI have been identified such as elevation of cardiac markers, especially Troponin T (tnT) on admission, and early resolution of the ST-segment...
elevation. Thus, several studies have shown an independent prognostic value of elevated tnt on admission in patients with STEMI treated with fibrinolytics.\textsuperscript{2–4} Even when treated with primary percutaneous coronary intervention (PCI), patients with elevated Troponin T or I levels on admission had a three to four times higher short- and long-term mortality.\textsuperscript{5,6} In patients treated for STEMI, also early ST-segment resolution is associated with a better outcome.\textsuperscript{7,8} Based on improved early infarct-related artery patency,\textsuperscript{9,10} smaller infarct size\textsuperscript{11} and less impairment of left ventricular function.\textsuperscript{12} Furthermore, ST-segment resolution has recently been shown to be superior to the thrombolysis in myocardial infarction-flow grade in predicting clinical outcome.\textsuperscript{13}

However, the combination of these two early available markers for predicting risk has not previously been evaluated. Therefore, the aim of this study was to evaluate admission tnt and ST-segment resolution separately and in combination for early risk stratification in STEMI patients treated with fibrinolytics.

**Methods**

**Patients and study design**

The present study was a substudy of the ASSENT-2 (ASsessment of Safety and Efficacy of a New Thrombolytic) trial\textsuperscript{14} and the ASSENT-PLUS trial.\textsuperscript{15} In brief, the ASSENT-2 trial was a prospective, worldwide multicenter trial in which 16 949 patients were randomized to a new single-bolus thrombolytic, tenecteplase or front loaded alteplase. The primary end-point was all-cause mortality at 30 days and patients were recruited between 1997 and 1998. In the ASSENT-PLUS trial 434 patients were recruited in Scandinavia and USA during 1999 and 2000. The study was designed to evaluate the efficacy and safety of alteplase as an adjunct to alteplase compared to routine heparin treatment.

In both studies inclusion criteria were symptoms of acute myocardial infarction within 6 h of onset, ST-elevation ≥0.1 mV in two or more limb leads, or ≥0.2 mV in two or more contiguous precordial leads, or left bundle branch block and age ≥18 years. Exclusion criteria in both trials were the regular ones for thrombolytic treatment and have been described in detail previously.\textsuperscript{14,15} One thousand, four hundred and fifty-six patients in total were enrolled in the ASSENT-2 and ASSENT-PLUS trials at Swedish hospitals out of which 881 had an admission tnt sample available (with 8.6% one-year mortality) and 864 patients without bundle branch block were included for continuous ECG-monitoring. Of the 864 patients with continuous ECG-monitoring, 112 (14.6% one-year mortality) were excluded due to time criteria (see below) or bad quality, and the remaining 752 patients had a one-year mortality of 6.6%.\textsuperscript{8} The 516 patients (386 from the ASSENT-2 and 130 from the ASSENT-PLUS trial) who had both of these variables available constituted the study population for the present substudy.

**Blood samples for biochemical markers**

Venous blood samples were collected before start of thrombolytic and anti-coagulation therapy. After centrifugation the EDTA-plasma samples were stored frozen at −70 °C for central analysis of tnt and myoglobin. Tnt was analysed with the third-generation tnt assay on an Elecsys 2010 with a detection limit of 0.01 µg/l. The mean intraassay CVs were 7.9% and 3.1% in the range <0.05 µg/l and 0.05–0.15 µg/l, respectively, and the mean interassay CVs were 11.2% and 5.1%, respectively. Based on a prospectively defined cut-off level the patients were divided into two groups, tnt ≤0.1 µg/l (tnt (−)) and ≥0.1 µg/l (tnt(+)).\textsuperscript{3,5}

**ST-segment resolution**

In the present substudy, 371 and 145 patients without bundle branch block were monitored for 24 h after admission by continuous vectorcardiography (VCG) and continuous 12-lead ECG, respectively. These two ST-monitoring methods have previously been shown to identify the same risk-groups among patients with unstable angina or non-q-wave infarction\textsuperscript{16} as well as in patients with STEMI.\textsuperscript{8} Patients had to have ≥30 min delay between thrombolysis and start of monitoring and had to be monitored at least 70 of the first 90 min or 3 of the first 4 h or 20 of the first 24 h to be included in the substudy. Methods for acquisition of continuous VCG and ECG recordings and for assessment of ST-segment measurements in this substudy have previously been further detailed.\textsuperscript{8} The patients were divided in two groups according to the ST-segment resolution from the maximal ST-elevation, measured at 60 min after start of recording, <50% ST-segment resolution (no ST-res60) and ≥50% ST-segment resolution (ST-res60).\textsuperscript{8} In addition, we also assessed time to 50% ST-segment resolution to evaluate its relation to admission tnt levels.

**Clinical end-points**

The outcome events in this substudy were all-cause mortality and re-infarction at 30 days and mortality at one year. The definition of re-infarction in the ASSENT-2 and ASSENT-PLUS trials has previously been described in detail.\textsuperscript{17} Event rates at 30 days were collected at a follow up visit while the one-year mortality was evaluated by patient records and telephone contacts. Data for all patients was recorded at 30 days and three patients were lost to follow up at one year.

**Statistical analysis**

Baseline characteristics were expressed as medians (with 25th–75th percentile) or percentages. Differences in proportions were evaluated with chi-square tests. T-tests were used to compare normally distributed continuous variables and Mann–Whitney U-tests were used to compare not normally distributed continuous variables. Correlations were assessed by the Spearman’s rank statistics. Independent predictors of one-year mortality were identified with a stepwise multiple logistic regression model including tnt(+) and no ST-res60, age, time from symptom onset to treatment, heart rate, systolic blood pressure (SBP), Killip class, infarct location and myoglobin level at admission. Variables with a P-value of less than 0.05 were entered in the model and variables with a value of more than 0.1 were removed. The independent predictors of one-year mortality as well as tnt(+) were then evaluated in a multiple logistic regression model. Additional logistic regression analyses were performed to adjust for study (ASSENT-2 or ASSENT-PLUS) and to test for the interaction between tnt(+) and no ST-res60. A clinical risk index, previously described by Morrow et al.\textsuperscript{18} (heart rate x[age/10]−2)/systolic blood pressure) was calculated for each patient with a heart rate between 50 and 150\textsuperscript{18} for evaluation of it’s interaction with tnt and ST-res60. According to Morrow et al.,\textsuperscript{18} this risk index was used to dichotomize patients into a low-risk group (Morrow-index <22.5) and a high-risk group (Morrow-index ≥22.5). In all statistical analyses, a P-value of less
than 0.05 was considered significant. All statistics were calculated with SPSS software (version 11.0, Statistical Package for the Social Sciences).

Results

Baseline characteristics

Clinical characteristics at baseline and mortality rates in the ASSENT-2, ASSENT-PLUS and the present substudy are shown in Table 1. The short- and long-term mortalities were lower in the present study compared to the ASSENT-2 trial, despite a higher median age in our substudy. Half of the patients (n=257) had no detectable tnT level on admission and the others (n=259) had a median level of 0.08 µg/l (25th–75th percentile, 0.03–0.23 µg/l).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics and clinical outcomes in the Assent-2, Assent-plus and the present substudy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable (%)</td>
<td>Assent-2 (n=16949)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>61 (52–70)</td>
</tr>
<tr>
<td>Male gender</td>
<td>76.9</td>
</tr>
<tr>
<td>Time to therapy (min.)**</td>
<td>162 (114–228)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>44.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38.2</td>
</tr>
<tr>
<td>Previous MI**</td>
<td>15.8</td>
</tr>
<tr>
<td>Anterior MI**</td>
<td>39.8</td>
</tr>
<tr>
<td>SBP (mmHg)**</td>
<td>133 (120–150)</td>
</tr>
<tr>
<td>Heart rate (bpm)**</td>
<td>72 (62–85)</td>
</tr>
<tr>
<td>Killip class=1</td>
<td>12.9</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>6.2</td>
</tr>
<tr>
<td>One-year mortality</td>
<td>9.6</td>
</tr>
<tr>
<td>Re-infarction by 30 days</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*386 patients from Assent-2 and 130 patients from Assent-plus.
**median (25th–75th percentile).
MI=myocardial infarction.
SBP=systolic blood pressure.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical characteristics according to Troponin T levels on admission and ST-segment resolution at 60 min (n=516).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable (%)</td>
<td>Troponin T (tnT&lt;0.1 µg/l)</td>
</tr>
<tr>
<td>n</td>
<td>400 (77.5%)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>66 (56–74)</td>
</tr>
<tr>
<td>Male gender</td>
<td>72.8</td>
</tr>
<tr>
<td>Time t ther. (min.)**</td>
<td>135 (95–200)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>31.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30.5</td>
</tr>
<tr>
<td>Previous MI**</td>
<td>17.5</td>
</tr>
<tr>
<td>Anterior MI**</td>
<td>39.6</td>
</tr>
<tr>
<td>SBP (mmHg)**</td>
<td>140 (126–156)</td>
</tr>
<tr>
<td>Heart rate (bpm)**</td>
<td>67 (58–79)</td>
</tr>
<tr>
<td>Killip class=1</td>
<td>11.3</td>
</tr>
<tr>
<td>Peak CKMB &gt;2 U</td>
<td>93</td>
</tr>
<tr>
<td>Myoglobin (µg/l)**</td>
<td>76 (50–162)</td>
</tr>
<tr>
<td>PCI performed</td>
<td>13.3</td>
</tr>
</tbody>
</table>

*Median (25th–75th percentile).
Time t ther.=time to therapy; MI=myocardial infarction; SBP=systolic blood pressure; U=upper reference limit; PCI=percutaneous coronary intervention.
ST-res60 \((n=215, 41.7\%)\) and consequently the majority no ST-res60 \((n=301, 58.3\%)\). Patients without ST-res60 had longer time from symptom onset to therapy and higher probability of previous myocardial infarction compared to the others.

**Relation between tnt and ST-segment resolution**

There was a weak positive correlation between tnt levels and time to 50% ST-resolution \((r=0.12, P=0.008)\) (Fig. 1). Compared to patients with tnt(−), patients with tnt(+) were less likely to achieve ≥50% ST-segment resolution at 60 min \((44.3\% \text{ vs } 32.8\%, P=0.03)\) and at 180 min \((85.5\% \text{ vs } 65.5\%), P<0.001)\).

**Outcome in relation to tnt and ST-segment resolution**

Patients with tnt(−) had a lower 30-day and one-year mortality compared to those with tnt(+), 2.0% vs 9.5% \((P<0.001)\) and 4% vs 13% \((P<0.001)\), respectively (Fig. 2). There was a positive correlation between tnt levels and duration of symptoms \((r=0.32, P<0.001)\). However, there was no statistically significant difference in one-year mortality between tnt(+) patients with symptom duration <2 (9.5%), 2–4 (14.6%) and 4–6 h (13.0%) \((P=0.85)\).

Patients with ST-res60 had a lower 30-day and one-year mortality than those without ST-res60, 0.9% vs 5.6% \((P=0.005)\) and 2.8% vs 8.4% \((P=0.009)\), respectively (Fig. 2). High and low risk patients were well identified with both ST-monitoring methods.

There was a weak positive correlation between time to 50% ST-segment resolution and duration of symptoms \((r=0.16, P<0.001)\). The mortality at one year tended to increase with longer symptom duration in patients without ST-res60; <2 (2.4%), 2–4 (10.6%) and 4–6 h (11.1%) \((P=0.06)\), respectively. Furthermore, the proportion of patients in the group without ST-res60 that achieved ST-segment resolution at 180 min, decreased with longer symptom duration, <2 (73.8%), 2–4 (69.9%) and 4–6 h (56.2%) \((P=0.045)\), respectively.

There was no difference between tnt(−) and tnt(+), 4.8% vs 4.3% \((P=0.84)\) or ST-res60 and no ST-res60, 5.1% vs 4.3% \((P=0.67)\) regarding re-infarction at 30 days (Fig. 2).

In a multiple logistic regression analysis no ST-res60 \((O.R. 3.53; 1.31-9.48)\), age, heart rate and SBP were independently related to one-year mortality (Table 3). Tnt(+) tended also to be independently related to one year mortality \((O.R. 1.95; 0.84-4.51)\). The result was similar in relation to 30-day mortality \((O.R. \text{ for } tnt(+) =2.57; 0.89-7.51, P=0.08)\). Also when adjusting for study, (ASSENT-2 or ASSENT-PLUS) the results were unchanged.

**Combination of admission tnt and ST-segment resolution**

There was a profound difference in 30-day mortality between the group with tnt(+) and without ST-res60, and the group with tnt(−) and with ST-res60; 12.8% vs 0.6% \((O.R. 22.7; 3.0-174.2, P<0.001)\). As shown in Fig. 3a, this profound difference in mortality was still present at one year; 18.2% vs 2.8% \((O.R. 6.4; 2.4-17.2, P<0.001)\). There was, however no statistically significant interaction between tnt and ST-res60 \((P=0.12)\). Fig. 3b illustrates a combination of our tnt and ST-res60 indices with Morrows’ clinical risk index\(^{18}\) in the patients eligible for
this index \( (n=487) \). Patients with a Morrow-index >22.5 and \( \text{tnT}(+) \) and without \( \text{ST-res} \leq 60 \) compared to those with a Morrow-index \( \leq 22.5 \) and the other combinations of \( \text{tnT} \) and \( \text{ST-res} \) had a one-year mortality of 25.0% vs 2.3% (O.R. 14.3; 4.8–42.3, \( P <0.001 \)).

Discussion

Outcome in relation to \( \text{tnT} \) and \( \text{ST-segment resolution} \)

Elevated \( \text{tnT} \) on admission in the present study was associated with a 3 to 4 times higher short- and long-term mortality in \( \text{STEMI} \) patients treated with fibrinolytics as in previous studies.\(^2\)–\(^4\) Moreover, the Odds Ratio of around two for elevated \( \text{tnT} \) in relation to mortality was similar in our study and in the large \( \text{Gusto-III} \) substudy\(^6\) after adjustments. Thus, the fact that \( \text{tnT}(+) \) was not an independent predictor of mortality in our study are probably explained by the relatively small sample size and few events. The proportion of patients with ‘elevated’ \( \text{tnT} \) was in the present study 22.5% compared to 8.9% in the \( \text{Gusto-III} \) substudy\(^4\) and 58% in a single-center study.\(^5\)

Reasons for the different proportions of ‘elevated’ \( \text{tnT} \) might be differences between the \( \text{tnT} \) methods used, chosen cut-off levels and symptom durations. In the \( \text{Gusto-III} \) substudy\(^4\) a first generation qualitative \( \text{tnT} \)-test with a sensitivity threshold of 0.2 µg/l was used while we used the third generation quantitative assay with a cut-off level of 0.1 µg/l. The mean symptom duration was 168 min in our study compared to 357 min in the single-center study.\(^5\)

We found a positive correlation between symptom duration and \( \text{tnT} \) level which was in accordance with previous studies.\(^4\) However, among the relatively few \( \text{tnT}(+) \) patients in our study, there was no significant difference in mortality in relation to short and long symptom duration, as in the \( \text{Gusto-III} \) substudy.\(^4\) Explanations for this might be that \( \text{tnT}(+) \) patients with short symptom duration may have had episodes of ischemia with release of \( \text{tnT} \) before onset of symptoms of the actual infarct and different thresholds of pain perception as suggested by Ohman et al.\(^4\) Thus, in the former cases the index infarct might be an early re-infarction which has been shown to be associated with adverse outcome.\(^19\) \( \text{TnT}(-) \) patients with long symptom duration on the other hand, may have had ischaemic preconditioning resulting in less or no \( \text{tnT} \) release.
ST-segment resolution at 60 min was in the present study independently associated with short- and long-term mortality as in previous studies. The weak positive correlation between time to 50% ST-resolution and symptom duration might explain the somewhat diverging results in previous trials evaluating the relation between symptom duration and the proportion of patients with ST-resolution. Furthermore, patients without ST-res60 and symptom duration more than 2 h compared to less than 2 h had about four times higher one-year mortality. This finding might be explained by the facts that the patients without very early signs of reperfusion (i.e. without ST-res60) but with a short symptom duration of less than 2 h more often were tnT(−) and more frequently achieved ST-segment resolution at least within 180 min. Both these findings, have previously been associated with a smaller final infarct size and better outcome. Hence, this might indicate a greater extent of myocardial salvage as a result of shorter time to therapy, even in this group without very early ECG signs of reperfusion. However, only one large study has been able to show independent prognostic value of both symptom duration and late ST-segment resolution after adjusting for other risk factors.

As in previous studies there was no difference in the rate of re-infarctions at 30 days between the tnT(+) and tnT(−) groups (Fig. 2). Also, there were no differences in re-infarctions in relation to ST-res60 in the present study, which is in contrast to some but not all previous studies.

Relation between tnT and ST-segment resolution

The weak positive correlation between tnT levels and time to ST-segment resolution could more or less be explained by the higher tnT levels (Fig. 1). Thus, ST-segment resolution was less likely to be achieved in the tnT(+) compared to the tnT(−) group. This relation has previously been shown only in a small study by Frostfeldt et al., where the percentage ST-segment resolution was less in the group with tnT elevation. Since several recently published studies have shown that ST-segment resolution is a more sensitive marker of tissue level reperfusion than of epicardial flow, our finding might indicate impaired tissue level reperfusion also in patients with tnT elevation. Hence, an elevated tnT on admission that reflects an irreversible myocardial damage that is already present on arrival, probably makes complete tissue level reperfusion less likely. However, the fact that no ST-res60 was independently related to mortality and tnT(+) tended to be, and the weak correlation between tnT and time to ST-segment resolution, also suggests complementary pathophysiological mechanisms...
Troponin T and measurement of ST-segment resolution

Concerning their relation to mortality. Thus, it might be hypothesized that admission tnt represents an objective marker of ischemic time, independent of time from symptom onset. ST-segment resolution on the other hand measures the effect of treatment on tissue level reperfusion, and subsequent myocardial salvage.

Combination

The combination of these two markers improved risk stratification. Thus, one third of the tnt(+) patients and two thirds of the patients without ST-res60, could be stratified into low to intermediate risk groups (Fig. 3a). Interestingly, the one third (38/115) of the tnt(+) patients with ST-res60 had a similar one year mortality as the tnt(−) group of patients with ST-res60 (Fig. 3a). Accordingly, a low risk group could be identified among the tnt(+) patients which to some extent might be explained by early tissue level reperfusion as indicated by ST-res60. Similarly, a possible reason for the better outcome in tnt(−) vs tnt(+) patients without ST-res60 might be the higher frequency of ‘later’ reperfusion, ST-segment resolution at 180 min, in the former group (74% vs 48.7%, P<0.001).

As in previous trials,1,4,18 the variables age, heart rate and SBP constituting the risk index proposed by Morrow et al.18 were strong independent predictors of mortality. The fact that no ST-res60 was and tnt(+) tended to be independently related to mortality, in addition to these variables, further supports the predictive capacity of admission tnt and ST-res60 (Table 3). Thus, by combining tnt, ST-res60 and the risk index,18 additional information of prognosis was obtained (Fig. 3b).

Study limitations

One limitation is that we investigated a STEMI population with low risk, despite the fact that patients were older compared to the entire ASSENT-2 study population (Table 1) and patients in other fibrinolytic trials.25 The mortality among all patients with available admission tnt (n=881) was similar to the entire Assent-2 study population in contrast to the lower mortality among all patients with calculated ST-segment resolution (n=752). Thus, the patients with analyses of ST-parameters were at lower risk in accordance with other studies evaluating ST-segment resolution.7,12,20 One explanation is the time criteria for ST-monitoring which excluded some of the patients with fatal events during their high risk period.14,24 Also patients with left bundle branch block, a high risk group25 were prospectively excluded from ST-monitoring.

Conclusions and implications

Tnt on admission and ST-segment resolution at 60 min are strong predictors of mortality and the combination of them gives additive early information about prognosis and further improves risk stratification in STEMI. An approach for risk stratification and treatment strategy can be suggested from our findings:

- A negative troponin T at admission, tnt(−), but no ST-res60, indicative of failed epicardial and/or tissue level reperfusion, occurred in 40% of the patients. These patients have a moderate mortality risk.
- An early ST-resolution as indicated by ST-res60, and either tnt(−) or tnt(+) also occurred in 40%. These patients are at low risk. Thus, their treatment seems sufficient.
- Finally, a positive troponin T at admission, tnt(+), and no ST-res60 occurred in 20%. These patients are at particularly high risk of death, and improvement of pharmacological and invasive treatment seems warranted.

Such an approach to risk stratification and treatment strategy needs to be tested in a prospective trial.

Acknowledgements

This study was supported by grants from the Swedish Heart and Lung Foundation; Boehringer Ingelheim, Skärholmen, Sweden; Ortizius AB, Täby, Sweden and GE Medical Systems, Information Technologies, Milwaukee, USA.

We wish to thank the research nurses Catrin Henriksson and Jörgen Cronblad at the Dept of Cardiology in Uppsala, and Gerd Källström, Helena Svensson, Monika Eriksson, Gunilla Norman and Jenny Rössberg at the Ischemia Core-lab, Sahlgrenska University Hospital/ Östra, Göteborg for their invaluable support.

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