Time-dependent diagnostic performance of a rapid troponin T version 2 bedside test in patients with acute coronary syndromes

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In a prospective trial, the diagnostic performance of the second version of the troponin T rapid assay (Trop T; cutoff 0.2 µg/L) was compared with the quantitative cardiac-specific troponin T assay (cTnT ELISA; cutoff 0.1 µg/L) and other established cardiac markers such as CK, CK-MB activity, CK-MB mass and myoglobin. Additionally, a 30-day follow-up was performed to determine the suitability of the Trop T assay and the reference markers for short-term risk stratification. Two-hundred-and-eighty-six consecutive patients with chest pain and suspected acute myocardial infarction (AMI) were enrolled in two CCU departments. Serial blood specimens were taken at admission and at 3, 6, 12, 24, 48, 72 and 96 h after admission. According to the biochemical criterion CK-MB mass, the patients were classified as having AMI in 154 patients (54%), unstable angina (UAP) in 72 patients (27%) and no evidence for acute cardiac ischemia in 55 patients (19%). Analytical method comparison of Trop T with cTnT ELISA (cutoff 0.1 µg/L) showed a good agreement, Trop T yielded only 4% false-negative and 3% false-positive results. The diagnostic performance of Trop T for the detection of AMI was only slightly inferior compared to cTnT ELISA. Beyond 12 h after admission, Trop T and cTnT ELISA maintained a sensitivity close to 100%, whereas the sensitivity of the other cardiac markers decreased sharply. The diagnostic sensitivity of Trop T for the detection of minor myocardial damage in UAP patients was the same as for cTnT ELISA. Death within 30 days' follow-up occurred only in AMI patients with a positive Trop T test result within the first 6 h after admission. The admission Trop T and cTnT ELISA were the only significant biochemical predictors of major cardiac events. In conclusion, these data show that Trop T has similar diagnostic sensitivity as cTnT ELISA and is a useful tool to confirm acute or subacute myocardial infarction. Trop T is an excellent marker in detecting minor myocardial damage in UAP patients and is suitable for short-term risk stratification.

Key words: cardiac markers; cTnT ELISA; rapid Troponin T; sensitivity and specificity

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Acute coronary syndromes represent a spectrum in the severity of coronary artery disease from suspected unstable angina through acute myocardial infarction. In patients with these syndromes, the presence and amount of myocardial damage can be assessed from myocardial proteins appearing in the circulation. The recent availability of cardiac-specific troponin T (cTnT) and troponin I (cTnI) [1–5] presents an opportunity to improve clinical assessment over other cardiac markers such as routine serial CK testing [6, 7], creatine kinase-MB (CK-MB) [9–10] and myoglobin [11–15]. It is now well established that elevation of cTnT and cTnI in patients with acute coronary syndromes is an indicator of myocardial damage and identifies patients at increased risk for subsequent myocardial injury or death, irrespective of CK or CK-MB levels [16–20]. Cardiac troponin T or troponin I rises in blood to proportionally higher levels than cardiac enzymes like CK and CK-MB. Cardiac troponin stays elevated for a week or more and can be differentiated from its skeletal muscle isoform by immunological techniques. These developments have not only allowed the detection of myocardial infarction, but also of minimal myocardial damage in patients with unstable angina, thus far undetectable by other diagnostic methods. Earlier studies have shown that these patients are at higher risk for subsequent cardiac events [16–18, 21–25].

Quantitative cTnT ELISA testing by laboratory systems needs sample preparation and mostly sample transportation away from the point of care. To overcome these limitations an assay for rapid bedside detection of cTnT elevations has been developed and has become available for clinical use [26–30]. This qualitative (positive or negative) cardiac troponin T rapid assay (Trop T) makes a result available within 20 min. I.e. the time to positive Trop T result decreases, with increasing cTnT concentration. The clinical use of such test strip depends upon its diagnostic performance and practicability, compared with the quantitative cTnT testing performed in the central clinical chemistry laboratory. The aims of the present study were first to assess and compare the time dependent diagnostic performance of Trop T with that of the quantitative cTnT ELISA and other cardiac markers CK, CK-MB mass and myoglobin including a suggested combined measurement of cTnT ELISA and myoglobin. Especially, we investigated the agreement between the Trop T and cTnT ELISA and the learning curve effect of Trop T. Second, to determine whether Trop T was a useful tool at or nearby the CCU, i.e. at the point of care, and in the hands of multiple readers and to prove whether Trop T is suitable to predict subsequent cardiac events.

MATERIALS AND METHODS

Patients

Two-hundred-and-eighty-six consecutive patients with chest pain and suspected acute myocardial infarction were admitted to two coronary care units (Heidelberg, Germany, and Rotterdam, The Netherlands) were included. The study period was from June 1995 to May 1996. None had suffered a documented acute myocardial infarction (AMI) within the previous week. Patients admitted more than once during the study period were included only on their first admission. Eight serial blood samples were drawn: at admission and at 3, 6, 12, 24, 48, 72 and 96 h after admission.

Analytical methods

1. Cardiac troponin T was measured qualitatively using a whole blood rapid bedside test

(Trop T version 2, Roche Diagnostics, Mannheim, Germany) [28, 29]. The nominal detection limit of the assay was 0.2 μg/L; results were read visually after precisely 20 min. All Trop T readings were done without delay, i.e. very shortly after blood sampling. In Rotterdam readings were performed during 12 months in two phases by laboratory technicians (n = 20) of the Thorax laboratory, located nearby the CCU. Two phases can be distinguished: part of the Trop T data were gathered after an initial familiarisation; the other part was collected after an extra training period and under strictly standardized reading conditions. In Heidelberg the strip readings were performed within 3 months by two physicians at the CCU.

2. Quantitative Troponin T analysis was performed using an enzyme-linked immunosorbent assay (cTnT ELISA; cardiospecific Enzymun Troponin T version 2, Roche Diagnostics) [31] on an ES 600 automated analyser with streptavidin-coated tubes (Roche Diagnostics) The cutoff value for detection of AMI was 0.1 μg/L.

3. Creatine kinase and creatine kinase MB activities were measured at 30°C by means of a N-acetylcysteine-activated optimised ultraviolet test (Merck; Darmstadt, Germany). Creatine kinase MB activity was determined by immunoinhibition. The upper limits of the reference intervals of creatine kinase and creatine kinase MB activity are 110 IU/L and 14 IU/L respectively.

4. Creatine kinase MB mass concentration was measured by a microparticle enzyme immunoassay (Abbott Laboratories; Abbott Park, Illinois) using an automated analyser (Abbott IMx). We used 5 μg/L as an upper limit of the reference interval.

5. Myoglobin was determined by a commercially available immunoturbidimetric assay (Merck; Darmstadt, Germany). The upper limits of the reference interval are 64 μg/L for women and 76 μg/L for men.

Clinical classification

Two cardiologists examined independently the admission ECG for the initial diagnosis of acute myocardial infarction. If the results were discordant assessment by a third cardiologist was asked for. The cardiologists and the attending physicians were blinded for the Trop T and cTnT ELISA readings. The final diagnosis of AMI was based on the WHO criteria [32] using a time-dependent increase of CK-MB mass above 5 μg/L as the biochemical criterion and ST segment elevation of at least 2 mm in 2 precordial leads or at least 1 mm in two extremity leads in the ECG. Thus, by definition, the sensitivity for AMI detection of CK-MB mass $\geq$ 5 μg/L was 100%. The group of patients with unstable angina (episodes of chest pain with ECG changes, but without elevated CK MB mass > 5 μg/L) was further subdivided into patients with or without minimal myocardial damage (MMD) and by an increased cTnT ELISA $\geq$ 0.1 μg/L [33].

Clinical data

Clinical data were recorded including previous cardiac history, classification of chest pain at hospital admission, admission clinical events, inhospital clinical course and medication at discharge. During a follow-up of 30 days cardiac events such as (recurrent) myocardial infarction, documented by ECG changes and CK-MB mass elevations, cardiac death and noncardiac death or the need for a coronary angioplasty procedure (PTCA) or coronary artery bypass graft surgery (CABG) were registered in the hospital records and, if needed, by contacting the referral hospitals or the attending general practitioners.

Statistical methods

The diagnostic sensitivities for the detection of AMI were calculated non-cumulative from standard statistical formulas [34]. The boolean combination of cTnT ELISA and myoglobin result was regarded as positive if cTnT or myoglobin was positive, and negative if both cTnT and myoglobin were negative. Differences between sensitivity and specificity of the different markers at different times after onset of symptoms were calculated with the chi-squared test for differences in proportions. Relative risks (RR) with accompanying 95% confidence intervals (95% CI) were used to investigate whether the cardiac markers were predictive of mortality or MI. A confidence interval not including 1.0 was considered to be significant. Statistical comparisons associated with P values less than 0.05 were considered to be significant.

RESULTS

Patient demographics

The study collective comprised of 286 consecutive patients with chest pain and suspected myocardial infarction admitted to the CCU departments of Heidelberg and Rotterdam. There were no significant differences in baseline characteristics between the two centers. The mean age was 62 years (range 31–92 years) and 75% were male. The median time interval between onset of symptoms and admission was 3.5 h (0–23 h). The diagnosis of acute myocardial infarction (AMI) was confirmed in 154 patients (AMI prevalence 54%). Seventy-seven patients (27% of all) suffered from unstable angina (UAP). Thirteen patients (17% of the UAP patients; 5% of all) had elevated troponin T values, while maximum CK-MB mass values in the series remained <5 μg/L, and were thus classified as having minor myocardial damage (MMD). Fifty-five patients were classified as having no evidence for acute cardiac ischemia. Table I gives the baseline characteristics.

Method comparison of Trop T with cTnT ELISA

Fig. 1 shows the distribution of the analytic performance of Trop T as a function of the quantitative cTnT ELISA concentration in each of the corresponding blood samples. The x-axis shows the cTnT ELISA concentrations at class intervals of 0.10 μg/L in the range 0.00–2.00 μg/L. All samples with cTnT ≥ 2.00 μg/l are accumulated in the last test class. Positive results of Trop T rapid assay are shown in the upper field, negative ones in the lower fields. The numbers at the top or bottom of each column indicate the number of positive or negative results within each test class interval. The ascending curve shows the increasing percentage of positive Trop T results with increasing cTnT ELISA values: from 5% at cTnT ≤ 0.10 μg/L to 33% in the interval 0.10–0.19 μg/L, 67% in the interval 0.20–0.29 μg/L, increasing to 100% in case of cTnT values > 0.60 μg/L. The area of interest comprises the zone around the possible detection limit. Within this overlap zone of negative and positive results, 0.10–0.29 μg/L Trop T showed 28/53 (53%) positives, within 0.30–0.39 μg/L it showed 44/68 (65%) positive results. The 50% intersect for Trop T thus occurs just below cTnT 0.30 μg/L.

Diagnostic performance

The time course of the diagnostic sensitivity and specificity for the detection of AMI are illustrated in Fig. 2 for Trop T, cTnT ELISA, myoglobin and for a combination of myoglobin and cTnT ELISA in relation to the time after admission. At admission myoglobin had highest sensitivity. Up to 4 to 8 h after onset of symptoms the sensitivity of Trop T was slightly lower than that of cTnT ELISA (80% vs. 92%; $p = 0.02$). From 12 h onwards the sensitivities of Trop T and cTnT ELISA remained close to

TABLE I. Baseline demographics and clinical course.

Diagnosis at discharge	Total (n = 286)	AMI* (n = 154) 54%	UAP† (n = 77) 27%	Other (n = 55) 19%
Age (year)s	62	62	64	63
Male (%)	74	73	79	69
Time from onset of symptoms until admission (median hours)	3.5	3.5	3.75	3.5
History %				
Prior myocardial infarction	41	45	35	20
Prior CABG‡	12	10	16	11
Prior PTCA§	22	18	35	15
Risk factors %				
Hypercholesterolaemia	28	29	29	24
Diabetes	21	22	21	16

*AMI = acute myocardial infarction; †UAP = unstable angina pectoris; ‡CABG = Coronary artery bypass graft; §PTCA = Percutaneous transluminal coronary angioplasty.

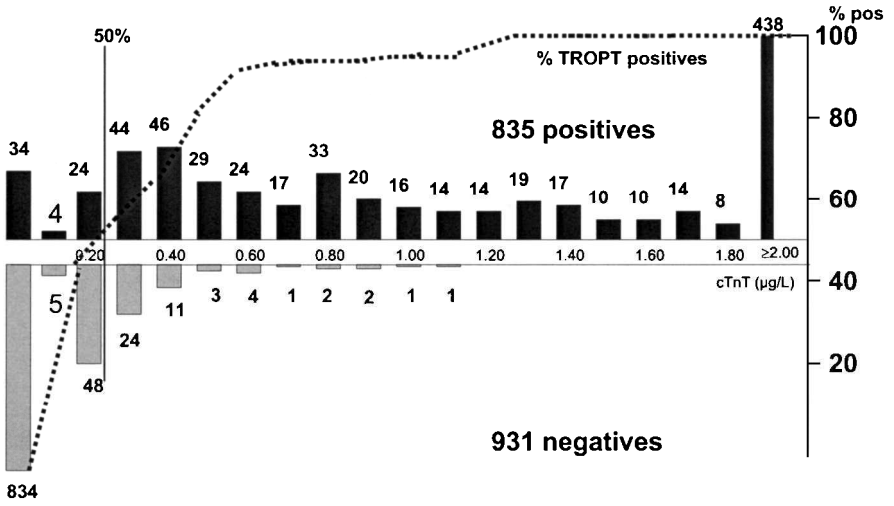

FIG. 1. Frequency distributions of Trop T-positive (upper field) and negative results (lower field) related to cTnT ELISA concentrations (abscissa) in 1766 samples.

100%, whereas the sensitivities of CK-MB mass and myoglobin decreased sharply. Myoglobin and CK-MB mass were initially most sensitive up to 8 h.

The specificities of Trop T and cTnT ELISA for detecting non-AMI remained similar during the whole time from onset of symptoms up to 96 h (85% to 95%) and were apparently less specific than CK and CK-MB mass (95% to 100%) (data not shown). The boolean combination of cTnT ELISA and myoglobin (positive if cTnT or myoglobin positive; negative if both are negative) resulted in an improved early sensitivity, albeit, at the cost of lower specificity (below 80%). Already at admission the sensitivity was 71% and increased within 3 h to 97%.

In the AMI patient group at least one of CK-MB mass values was by definition positive ($\geq$5 µg/ml) in 100% of the patients, followed by cTnT ELISA (96%) and Trop T (88%).

Of the 77 UAP patients 17% had an elevated cTnT ELISA and 14% a positive Trop T. CK-MB was by definition not elevated in these patients.

Learning curve

In Rotterdam readings were performed during 12 months by 20 clinical laboratory technicians in two phases, i.e., before starting the clinical study an extensive familarization program was run; midway, extra training was given especially for improving the faint marker line at the detection limit and strictly standardization reading conditions were introduced. In Heidelberg two physicians performed the readings within 3 months. It turned out that the Trop T needed a learning phase (Fig. 3). The study period was evenly divided in quartiles. The extra training in Rotterdam had a substantial influence on the analytical sensitivity (increase from 93% to 98%). Analytical specificity of the physicians decreased in the second half of the study from 99% to 91%.

Clinical events (30-days follow-up)

Table II gives the cardiac events within 30 days after admission according to the diagnosis at discharge (AMI, UAP or another diagnosis). Within 30 days, only patients with AMI and an early positive Trop T test (0 to 6 h after admission) died. As far as reinfarction and coronary intervention is concerned no significant differences depending on the Trop T result were found in the AMI group. In the UAP group, none of 66 patients with persistently negative Trop T results suffered from myocardial (re)infarction and 2 patients out of 11 patients (18%) with at least one positive Trop T test developed a (re)infarction.

Seven of the 13 UAP patients with MMD

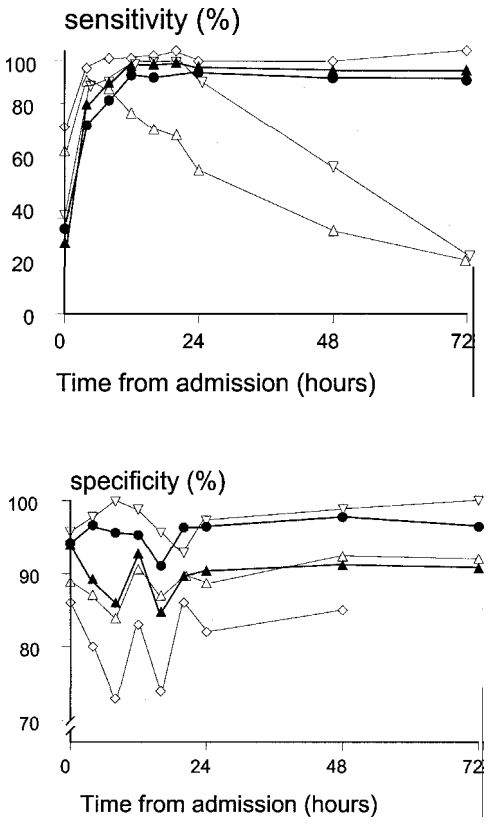

FIG. 2. The time course of the diagnostic sensitivities and specificities for the detection of acute myocardial infarction for Trop T, cTnT ELISA, myoglobin, CK, CK-MB activity, CK-MB mass, and a combination of myoglobin and cTnT ELISA in relation to the time after admission. ● TROP T, ▲ cTnT, ▽ CK-MB mass, △ Myoglobin, ◇ Positive: cTnT or myoglobin positive. Negative: cTnT and myoglobin negative.

(54%) underwent a coronary intervention (CABG or PTCA), whereas 20 out of 64 non-MMD patients (31%) underwent a coronary intervention. In the "other" patient group no major cardiac events were found.

All admission cardiac markers were univariate predictors of death or non-fatal myocardial infarction through day 30 (Table III). The combined endpoint of death, non-fatal infarction, CABG or PTCA occurred in 50% of the patients with a positive Trop T at admission compared to 32% of the patients with a negative test. The admission Trop T and cTnT ELISA were the only significant predictors of any major cardiac event.

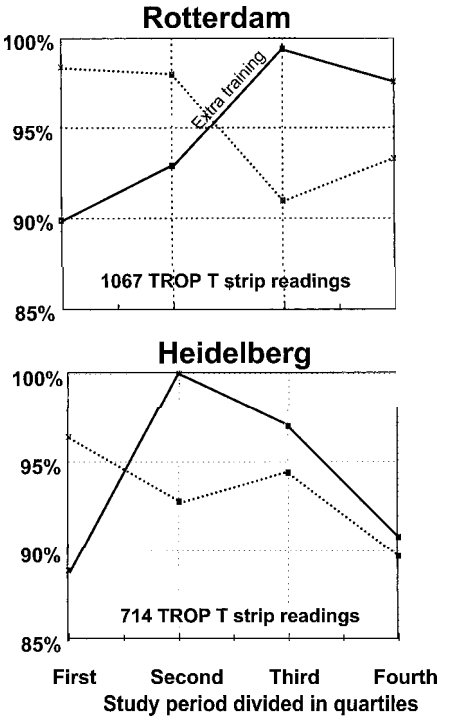

FIG. 3. Learning curve of the analytical sensitivity and specificity of Trop T throughout the study period. The study period was evenly divided in quartiles. -■-Analytical sensitivity. ••••• Analytical specificity.

DISCUSSION

The present study evaluated the diagnostic performance of Trop T in patients with acute coronary syndromes, as compared to quantitative cTnT ELISA and other established cardiac markers by extensive serial testing from admission up to 96 h. While quantitative troponin T testing with laboratory systems needs sample transportation and sample preparation, the qualitative rapid assay Trop T, tested in this study, allows bedside determination of troponin T only within 20 min after blood sampling. This study showed that Trop T has a comparable sensitivity for AMI and specificity for non-AMI to cTnT ELISA. Within 6 h after admission the sensitivity of Trop T was only slightly lower than that of cTnT ELISA, due to the twofold higher detection limit (0.2 μg/L vs. 0.1 μg/L) and false-negative readings. It turned out that training experience was important with this second version of Trop T. The learning curve

TABLE II. Cardiac events within 30 days after hospital admission (n = number of patients).

Diagnosis at discharge Result with Trop T	All diagnoses (n = 286)			AMI (n = 154)			UAP without MMD (n = 64)			UAP with MMD (n = 13)			Other (n = 55)		
	Positive in 0–6 h (n = 150)	Positive >6 h (n = 13)	Persistently negative (n = 121)	Positive in 0–6 h (n = 139)	Positive >6 h (n = 10)	Persistently negative (n = 5)	Positive in 0–6 h (n = 1)	Positive >6 h (n = 1)	Persistently negative (n = 62)	Positive in 0–6 h (n = 7)	Positive >6 h (n = 2)	Persistently negative (n = 4)	Positive in 0–6 h (n = 2)	Positive >6 h (n = 0)	Persistently negative (n = 53)
Death	12 (8%)	0 (0%)	0 (0%)	12 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
(Re)infarction	10 (7%)	3 (15%)	1 (1%)	10 (7%)	2 (20%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CABG	12 (8%)	0 (0%)	4 (3%)	12 (9%)	0 (0%)	1 (13%)	0 (0%)	0 (0%)	3 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PTCA	43 (29%)	3 (15%)	18 (15%)	39 (32%)	1 (10%)	1 (13%)	0 (0%)	0 (0%)	17 (27%)	3 (43%)	2 (100%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)

For the abbreviations, see Table I.

(Fig. 3) does illustrate that nicely. Visual detection of a positive Trop T at the cutoff limit was especially prone to interobserver variability around the detection limit. Besides the eye sensitivity and the experience of the observer, the type of light (sunlight, artificial light), the incidence of the light (direct, indirect) and the eventual use of a reading lamp definitely affected Trop T readings. Therefore, extra training was given midway in Rotterdam. In parallel, test strip reading conditions were standardized by introducing a reading lamp and by instructing the technicians to carefully inspect test strips with faint marker lines at 20 min under different corners of light incidence. In the fourth quartile of the study period, more positive Trop T results were found, both correct and incorrect. Consequently, the analytical sensitivity increased whereas the analytical specificity decreased almost by a similar percentage. In Heidelberg, no extra training was given. The two physicians who did the readings reached almost 100% sensitivity in the second quartile of the study period. Surprisingly, both analytical sensitivity and specificity declined to about 90% in the last quarter. The authors speculate that after an initial period of attentive visual inspection, some habituation appeared, leading to an increased number of false-positives and false-nagatives. In summary, the very faint marker line of the second generation Trop T test strips in case of troponin T concentrations around the cutoff limit clearly hampered correct reading and surely explains a great deal of the discrepant readings.

At the time of the study only one antibody existed. We may speculate that some of the discrepancies between Trop T and cTnT ELISA resulted from cross reactivity of the one unspecific antibody with skeletal troponin T. However, in our opinion, this did not contributed essentially to the relative high number of the "false-positives". At present, this problem has been solved by the existence of more antibodies.

This investigation has used the second version of Trop T. After this study was finished (in 1996) a third generation of Trop T has been developed [35]. The latest version of both visual and electronically read Trop T have the same cutoff (0.1 μg/L) as the quantitative cTnT ELISA. Notwithstanding, the authors are con-

TABLE III. Admission cardiac markers as predictors of mortality, myocardial infarction, CABG and PTCA within 30 days after admission.

	Death		Death/MI		Death/MI CABG/PTCA	
	RR*	95% CI†	RR	95% CI	RR	95% CI
Trop T	10.4	2.3–48.0	2.9	1.3–6.8	1.5	1.1–2.1
cTnT ELISA	9.3	1.2–71.0	7.6	1.8–32.1	1.7	1.2–2.4
Myoglobin	4.2	1.0–17.3	2.7	1.0–7.1	1.3	0.8–2.3
CK-MB mass	13.2	4.3–41.2	4.9	1.9–12.7	1.3	0.8–2.3

*RR = relative risk; †95% CI = 95% confidence interval. For the other abbreviations, see Table I.

vinced that this study has still merit as visually read Trop T is still widely used in current clinical practice.

The early sensitivity of Trop T was similar to CK-MB mass, which had such a high sensitivity because it was used as classification criteria for AMI. Beyond 6 hours and up to 96 hours after admission the sensitivities of Trop T and cTnT ELISA remained close to 100%, whereas the CK-MB mass decreased sharply.

To rule out AMI on the basis of cardiac markers, some time is needed for the marker released from necrotic cells to reach the circulating blood and to rise above the upper reference limit of the assay used, as well as for the pre-analytical, the analytical and reporting phases in the specific hospital setting [36–38]. The use of new cardiac markers may increase sensitivity, which may result in a more frequent diagnosis of myocardial damage. However, it is still controversial whether serial testing improves the prediction of hospital mortality [39, 40]. In this study AMI patients with an early (up to 6 h after admission) positive result for Trop T had a significantly higher risk of death than patients with a late positive or persistently negative result.

Furthermore troponin T detects minor myocardial damage in patients after an episode of acute myocardial ischemia even when the WHO criteria for an acute myocardial infarction are not fulfilled [22–26]. The latter is the reason for the relatively poor specificity for the former diagnosis based on "AMI" of Trop T or cTnT ELISA compared to CK-MB mass. However, several studies provided firm evidence that these patients with MMD were at high risk for cardiac events [24, 41–43]. This study also showed that the diagnostic sensitivity of the Trop T rapid test for the detection of high-risk UAP patients with MMD was nearly the same as for cTnT ELISA. In UAP patients with a positive Trop T test the percentage of cardiac events was higher than in the Trop T negative group.

The study diagnostic sensitivities for Trop T, cTnT ELISA and conventional cardiac markers for detection of massive acute and subacute myocardial infarction and minimal myocardial damage change rapidly in the early hours after onset of symptoms, as reported earlier [36]. In this study the highest efficacy to detect AMI was obtained with the use of a combination of the cTnT ELISA and myoglobin, apparently at the expense of a lower specificity. Myoglobin alone had a relatively high sensitivity in the first 3 to 6 h, albeit its specificity was low. The same results were seen in several other studies [44–50]. After 6 h both troponin T and CK-MB mass had the highest diagnostic sensitivity in the AMI group. The latter markers appear not to be suitable as early markers for ruling out AMI. Trop T had similar diagnostic sensitivity as cTnT ELISA. The measurement of troponin T is especially important at 6–24 h from symptom onset. At this time, a positive result will identify all patients with acute myocardial infarction and also patients with unstable angina, who have sustained minor myocardial damage. We agree with a recent proposal which recommended a strategy which included utilisation of two biochemical markers for routine AMI diagnosis [51, 52]: an early, unspecific marker such as myoglobin (reliably increased in blood within 6 h after onset of symptoms) and a late, cardiospecific marker such as troponin T (relative late appearance in blood but with high sensitivity and specificity for myocardial injury and remaining abnormal for many days after onset).

CONCLUSION

These data show that Trop T has similar diagnostic sensitivity as cTnT ELISA and is a useful tool to confirm acute or subacute myocardial infarction. It can be performed conveniently in a 'field' situation, such as in the hands of minimally trained physicians, as well as clinical chemistry laboratory technicians. The rapid Trop T assay at the point-of-care allows a qualitative determination from whole blood with a turn-around-time of only 20 min. The diagnostic performance of the Trop T test strip is nearly similar to that of the quantitative cTnT ELISA and is superior compared to CK-MB mass and the cardiac enzymes in unstable angina patients with minimal myocardial damage.

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