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Utility of the Immediate 2-Dimensional Echocardiography and Troponin T Test Combination for Diagnosing Non-ST Elevation Acute Coronary Syndromes in Patients with T-Wave Negative and Non-Diagnostic Electrocardiogram

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Introduction: In a cohort of patients with chest pain and a negative troponin T (TnT) test, a mortality rate of 1.4 % during a mean follow-up of 9–10 weeks was recently reported. The mortality was greater in patients with evidence of ischaemic ECG changes and a negative TnT test (1.6–4.4 %). Few studies have examined the efficacy of two-dimensional echocardiography (2DE) in patients with chest pain. The purpose of the present study was to determine the clinical utility, sensitivity, and specificity of the combination of TnT levels and 2DE in patients presenting with chest pain, T-wave negative and non-diagnostic ECG on the entry ECG.

Methods: 88 consecutive patients with chest pain and the presence of T-wave inversion, and non-diagnostic ECG, an acceptable 2DE window, evidence or no evidence of alterations of the segmentary motion, a negative or positive TnT test, and normal value of CK, CK-MB, were enrolled. 2DE, blood CK, CK-MB, and TnT levels were controlled at entry and subsequent samples were obtained every 4 h for the first 12 h and then every 12 h. A haemodynamic study was performed in all patients within 12–72 h of admission. Percutaneous transluminal coronary angioplasty or coronary artery bypass graft were performed according to angiographic findings and left ventricular function.

Results: A total of 88 patients, who met the entry criteria, were divided as follows: group 1: T-wave inversion (36 patients); and group 2: non-diagnostic ECG (52 patients). The combination of positive TnT and wall motion alterations showed a higher sensitivity and higher predictive values in comparison with TnT alone. Patients with concordance between TnT and 2DE were at higher risk. Patients with a negative combination in all groups (50 patients) showed a moderate incidence of critical coronary stenosis (20 %), as well as a negative 2DE alone (52 patients) (10 %). Patients with a negative TnT (70 patients) showed higher incidence of critical coronary stenosis (28 patients).

Conclusion: Our results suggest that the combination of a negative TnT test and negative 2DE in patients presenting to emergency department with chest pain and T-wave inversion or without ECG changes is a useful tool to identify those who can be discharged safely. On the other hand, our data is important to identify the high risk (when positive) patients, and to reduce the number of false negative diagnoses. *J Clin Basic Cardiol* 2005; 8: 37–42.

Key words: acute coronary syndromes, coronarography, echocardiography sensitivity, troponin T

Patients with acute coronary syndromes (ACS) have varying levels of risk of suffering unfavourable outcomes. Many diagnostic approaches have been used for evaluation of patients with chest pain, but patients without ST segment changes on ECG are more difficult to assess.

Prospective studies of troponin T (TnT) assays in ACS have demonstrated that TnT has better diagnostic accuracy than creatinine-kinase-MB. Unfortunately, in a cohort of patients with chest pain and a negative TnT test, a mortality rate of 1.4 % during a mean follow-up of 9–10 weeks was recently reported. The mortality was greater in patients with evidence of ischaemic ECG changes and a negative TnT test (1.6–4.4 %) [1–5]. To avoid unnecessary admissions, current strategies entail accelerated diagnostic protocols, 6–12 h of monitoring, injury marker controls, and an early exercise test [6–8]. Recently, a study enrolling patients with chest pain showed that the TnT test had a sensitivity of 61 % and a specificity of 96 % at 6 h from admission. In addition, it was reported that sensitivity increased with time, reaching the highest values after 22 h [9]. Recently, it was reported that routine angiography has superior sensitivity to non-invasive tests.

This report raises the important question whether current diagnostic strategies are optimal for immediate diagnosis [10]. Few studies have systematically examined the efficacy of 2-dimensional echocardiography (2DE) in patients with

chest pain. Most studies have attempted to identify only those patients with acute myocardial infarction (AMI). The early identification of patients with ACS is also important; the number of patients with ACS has increased or else it is detected more often [11–15]. 2DE is a potentially useful and cost-effective imaging modality for the assessment of chest pain [11, 12]. The test is non-invasive, and diagnostic information is available within minutes [16–19]. When the 2DE is performed during an episode of chest pain, the absence of a segmental wall motion abnormality is evidence against ischaemia as the cause of chest discomfort, whereas the presence of a wall motion abnormality increases the likelihood of coronary artery disease (CAD) and is indicative of myocardial infarction, ischaemia, or both [20–23].

The purpose of the present study was to determine the clinical utility, sensitivity, and specificity of the combination of TnT levels and 2DE in patients presenting with chest pain and T-wave inversion and non-diagnostic ECG.

Materials and Method

Population

From December 2000 to February 2002, 88 consecutive patients were admitted to the study. All patients aged 18 years and older in whom chest pain was thought to be cardiac in origin by the admitting physician were enrolled. Informed consent was obtained from all patients.

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Eligibility Criteria

The presence of T-wave changes, and non-diagnostic ECG in patients presenting with chest pain (first episode) at rest, that was judged to be caused by ischaemia, an acceptable echocardiographic window, evidence or no evidence of concomitant alterations of the segmentary motion on 2DE, performed on admission, and evidence and no evidence of injury, as assessed by biochemical markers (TnT) (normal values 0.01–0.1 ng/ml), using quantitative testing (Boehringer Mannheim Corp.) at admission and in subsequent samples (4–8–12–24 h). Blood CK and CK-MB had to be within the normal range in the serial samples (4–8–12–24 h) obtained during hospitalisation.

Exclusion Criteria

A history of AMI, myocardial ischaemia precipitated by a disorder other than atherosclerotic CAD, persistent ST-segment elevation myocardial infarction, ST-segment depression, or new left-bundle branch block, ventricular hypertrophy, ventricular pacing, previous percutaneous transluminal angioplasty (PTCA), planned PTCA or coronary bypass surgery, a history of cardiomyopathy, or previous episodes of heart failure, 2DE of inadequate technical quality, and patients with a CK-MB exceeding normal or, when CK-MB was not available, a total CK greater than twice normal. In addition, patients with ST-segment alterations known to be pre-existing and attributable to coexisting disorders (e. g. left ventricular hypertrophy) or medication (e. g. digoxin) were also excluded.

Echocardiogram Variables

The variables that were analysed included right ventricular function and left ventricular systolic function (HP, Acuson, Vingmed). Data were stored on super VHS videotapes. The left ventricle was divided into 16 segments as previously described [24–26]. Each segment was classified in two ways: having either normal or abnormal systolic function. Abnormal systolic function was considered to be present in a segment if it manifested both abnormal motion (hypokinesia, akinesia, dyskinesia) and thickening. The right ventricular free wall image in the parasternal and apical views and the diaphragmatic wall in the subcostal view were divided into apical, middle, and basal segments. The right ventricular wall was separated into anterior and posterior segment in the parasternal short-axis view. Motion of the right ventricle wall was classified in the same way as for the left ventricle.

Treatment for Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction

All patients received our standard treatment (glucose, insulin, potassium), nitrates, unfractionated/low-molecular weight heparin, aspirin, clopidogrel/ticlopidine, and where possible metoprolol, and statins etc. Patients with a positive TnT test received glycoprotein (GP) IIb/IIIa receptor antagonists (abciximab 12 h, tirofiban, and eptifibatide 48–72 h).

Study Design

At time of presentation to the hospital, a member of the study team obtained a detailed history and performed a complete physical examination. In addition, a complete 12-lead ECG + V3R + V4R lead, and a sample of blood for serum enzyme measurements were obtained, and 2DE was performed. Subsequently, 2DE was carried out daily. All members of the study team had completed at least 4 years of internal cardiology residency and training in 2DE. Two observers, blinded to the clinical and ECG data, evaluated the 2DE images. In cases of discrepancy, the 2DE images were reviewed again, and a decision was made by consensus. The historical informations

used to evaluate the patients in this report included age, sex, and a history of hypertension, diabetes, and cigarette smoking, among other factors etc., and the Thrombolysis in Myocardial Infarction (TIMI) risk score [27]. The ECG and 2DE were classified as normal or abnormal (as previously reported). Treatment with GP IIb/IIIa receptor inhibitors was performed when alteration of segmentary motion were observed without ECG alterations and a positive TnT test, and when only T-wave inversion and non-diagnostic ECG with a positive TnT without 2DE alterations were present. The presence of a quantitatively positive TnT test led to a GP IIb/IIIa inhibitor treatment [28].

All patients were continuously monitored, heart rate, 2DE, and ECG were recorded daily. Blood CK and TnT levels were determined every 4 hours for the first 12 h and then every 12 h. Coronarography was performed in all patients within 12–72 h from admission according to treatment received (abciximab, tirofiban, eptifibatide, unfractionated heparin or low-molecular weight heparin, aspirin, clopidogrel/ticlopidine, beta-blockers, nitrates, statins). PTCA or CABG were performed according to angiographic findings and left ventricular function. Significant CAD was defined as > 50 % left main stenosis, or > 70 % stenosis in a major coronary artery or its branches. Physicians who performed haemodynamic tests and laboratory measurements were blinded to the clinical data, ECG data, and the 2DE images. All data was evaluated and analysed by an independent blinded physician.

Statistical Analysis

The data are expressed as mean \pm SD. Calculation of the sensitivity, specificity, and predictive values was performed according to the usual formulae. Continuous and categorical data were compared using T test and chi square analysis. The 95 % confidence interval (CI) was calculated to evaluate the sensitivity, specificity, and predictive values (negative and positive). A p-value < 0.05 was considered to be significant. The Kendall concordance coefficient was calculated to evaluate the concordance of the tests with coronary angiography.

Results

Among 448 consecutive patients screened, 88 patients met the entry criteria and agreed to be enrolled (characteristics listed in Table 1). They were divided as follows:

Table 1. Data of all the enrolled patients at entry, divided according to ECG presentations

ECG	Non-diagnostic	T-wave inversion
Patients (n)	52	36
TnT +	14	4
TnT –	38	32
2DE +	22	14
2DE –	30	22
CAG +	28	14
CAG –	24	22
1V	12	12
2V	4	/
3V	12	/
LMCA	/	2
PTCA	14	12
CABG	14	2

TnT = troponin T; (+) = positive; (–) = negative; 2DE = echocardiogram; CAG = coronary angiography; V = vessel; LMCA = left main coronary artery; PTCA = percutaneous transluminal coronary artery; CABG = coronary artery by-pass grafting

Table 2. Group of patients with T-wave inversion at entry ECG

	TnT +	TnT -	2DE +	2DE -	CAG +	CAG -
Patients (n)	36	4	32	14	22	14
Age (years)	60.2 ± 12.4					
Sex (♂/♀)	24/12					
TnT +/Echo +	4		4		4	
TnT -/Echo +		10	10		8	2
TnT -/Echo -		22		22	2	20
Echo +			14		12	2
TnT +	4				4	
Echo -				22	2	20
TnT -		32			10	22

TnT = troponin T; (+) = positive; (-) = negative; 2DE = echocardiogram; CAG = coronary angiography; Echo = echocardiogram

Group 1: patients with chest pain and T-wave inversion. This group consisted of 36 patients (12 ♀, 24 ♂), mean age 60.2 ± 12.4 years.

Group 2: patients with non-diagnostic ECG. This group consisted of 52 patients (18 ♀, 34 ♂), mean age 58.25 ± 7.2 years.

Group with T-Wave Inversion (36 Patients)

Table 2 shows the results obtained in patients with T-wave inversion at entry. This group had a low incidence of positive TnT test (4 patients), while 2DE was positive (wall motion alterations) in 14 patients. The four patients with the combination of a positive TnT test and wall motion alterations showed significant critical stenosis on angiography and the same results were observed in 12 patients with positive 2DE, and all these patients required revascularisation procedures.

Patients with TnT negative test and positive 2DE showed high incidence of critical stenosis (8/10 patients).

On the contrary, patients with TnT and negative 2DE showed low incidence of critical stenosis on angiography (20/22 patients). Negative TnT alone showed high incidence of false negative (10/32), while negative 2DE showed low incidence of false negative (2/22 patients). Table 3 shows the sensitivity, specificity, and predictive values of TnT, 2DE and their combination. In this group 2DE and the combination (TnT + 2DE) showed higher values in sensitivity than TnT alone.

The TnT test alone showed a high specificity and positive predictive value. The negative predictive value was higher in the 2DE and in the combination (TnT + 2DE) groups. The concordance coefficient was more significant in the 2DE group and in the combination group than TnT test positive patients, $p < 0.0001$ and 0.0066 , respectively.

Table 4. Group of patients with non-diagnostic ECG at entry

	TnT +	TnT -	2DE +	2DE -	CAG +	CAG -
Patients (n)	52	14	38	22	30	24
Age (years)	58.25 ± 7.2					
Sex (♂/♀)	34/18					
TnT -/2DE +		10	10		10	
TnT +/2DE +	12		12		10	2
TnT +/2DE -	2			2	2	2
TnT -/2DE -		28		28	8	20
2DE +			22		20	2
TnT +	14				10	4
2DE -				30	8	22
TnT -	38				18	20

TnT = troponin T; (+) = positive; (-) = negative; 2DE = echocardiogram; CAG = coronary angiography

Group with Non-Diagnostic ECG at Entry (52 Patients)

Table 4 shows the results obtained in this group of patients. This group as well as the previous groups shows a low incidence of positive TnT test (14 patients), while the 2DE showed a higher incidence of wall motion alterations (22 patients). The positive combination of the two tests was observed only in 12 patients. All the 28 presenting critical coronary stenosis underwent revascularisation procedures. 2DE showed higher sensitivity, specificity, and predictive values in comparison with TnT alone. The combination (2DE + TnT) showed similar results (Tab. 4).

Patients with a negative TnT and a negative 2DE showed a moderate incidence of false negative (8/28 patients). Positive 2DE and negative TnT patients showed high incidence of critical stenosis at angiography (10/10 patients). The analysis of patients with only one test positive (TnT or 2DE) showed high incidence of critical stenosis (10/14 and 20/22, respectively). Two patients from the group with non-diagnostic ECG showed a positive TnT test with positive 2DE but the coronarography did not show critical stenosis. These patients did not show diseases, which might explain these results (pericardial, myocardial, renal, thyroid etc). In addition, other tests (myoglobin, CK etc.) were also negative. We hypothesised that these patients were suffering transient ischaemia in the coronary circulation, probably due to endothelium alterations with rapid reperfusion before determining micronecrosis (the 2 patients received abciximab treatment). In the first 6 months of follow up, these patients had further episodes of chest pain and subsequent coronarography did not show any change in comparison with the previous haemodynamic tests. Six patients had positive TnT or 2DE results (4 with positive TnT and 2 with positive 2DE), these patients had intermediate stenosis $< 70\%$ and in the follow-

Table 3. Sensitivity, specificity and predictive values of the troponin T (TnT), Echocardiogram (2DE) and their combination (TnT + and 2DE +, and TnT + plus 2DE +)

	TnT		2DE		2DE and TnT		2DE plus TnT	
T-wave inversion								
Sensitivity	28 %	19.72–37.43	85 %	78.86–92.57	28 %	19.72–37.43	85 %	78.86–92.57
Specificity	100 %		90 %	85.27–96.54	100 %		90 %	
Pos. Pred. V.	100 %		85 %	78.86–92.57	100 %		85 %	78.86–92.57
Neg. Pred. V.	68 %	59.67–77.83	90 %	85.27–96.54	68 %	59.67–77.83	90 %	85.27–96.54
Non-diagnostic ECG								
Sensitivity	35 %	26.32–45.11	71 %	62.57–80.28	35 %	26.32–45.11	71 %	62.57–80.28
Specificity	83 %	76.03–90.64	91 %	86.25–97.08	91 %	86.25–97.08	83 %	76.03–90.64
Pos. Pred. V.	71 %	62.57–80.28	90 %	85.27–96.54	83 %	76.03–90.64	83 %	76.03–90.64
Neg. Pred. V.	52 %	42.85–62.42	73 %	64.67–82.00	55 %	45.25–64.75	71 %	62.57–80.28

Pos. Pred. V. = Positive predictive value; Neg. Pred. V. = Negative predictive value

up at 6 months 3 patients showed recurrence of angina. The subsequent coronarography showed progression of the stenosis up to critical in all the 3 patients and PTCA was performed. The total wall motion score index was not measured because all the patients showed normal motion in the segments with motion alteration at entry within 48–72 h either before or after PTCA.

In both groups, the positive combination TnT and 2DE, 4/4 in T-wave inversion, 10/12 in the non-diagnostic ECG, identified a high risk group of patients. In fact, these patients showed important coronary stenosis. The most important result was that patients with negative combination in all groups (22 from group 1 and 28 from group 2), showed a moderate incidence of critical coronary stenosis (10/50 [20 %] patients), while patients with negative TnT (32 and 38, respectively) showed high incidence of coronary stenosis (28/70 patients). Patients with a negative 2DE alone (22 and 30, respectively), showed a moderate incidence of critical coronary stenosis (10/52 patients). The negative combination and 2DE alone appear to improve the detection of the patients without critical coronary stenosis ($p < 0.001$).

The analysis by the Kendall concordance coefficient (Tab. 5), calculated to evaluate the concordance of the tests with coronary artery angiography, either as single tests (TnT and 2DE) or in combination (2DE and TnT and TnT plus 2DE) showed that 2DE is better than both TnT alone and their combination (TnT plus 2DE) for early identification of patients with high risk of CAD presenting to hospital with chest pain on admission.

Discussion

In an era of cost containment, consideration also should be given to identification of patients at low risk for adverse cardiac events, who may be safely discharged without expensive inpatient hospitalisation. Chest pain symptoms alone account for more than five million patient visits annually to EDs. However, objective ECG evidence of myocardial ischaemia is present in only lightly more than one fourth of these patients, and a final diagnosis of an ACS is made in less than one fifth [29, 30]. If the ECG is non-diagnostic on admission it tends to remain non-diagnostic, with only some 10 % changing to ST elevation [31].

Although rapid evaluation of these patients, utilising sensitive biochemical markers of myocardial injury and predischarge exercise test, is now common practice, it remains uncertain whether such protocols adequately test for the presence of underlying CAD [32–34].

A recent study showed that immediate coronary angiography detected significantly more CAD than expected in low-risk patients [10]. In addition, this study demonstrated that the prevalence of CAD in low-risk patients is considerably greater than non-invasive testing suggests [35]. The multicenter chest pain study [36] showed that 4 % of patients at-

tending hospital for assessment of acute chest pain and who had documented AMI at presentation, or within 3 days, were sent home with the diagnosis of non-ischaemic chest pain. Gibler et al. [13] tried to improve identification of patients at risk used serial CK-MB mass testing, serial 12-lead ECG, 2DE, and graded exercise testing. Although TnT levels are accurate in identifying myocardial necrosis [37] such necrosis is not necessarily secondary to atherosclerotic CAD. Therefore in making the diagnosis of NSTEMI, cardiac TnT levels should be used in conjunction with appropriate symptoms or signs and/or ECG changes [28]. TnT levels should not be relied on as the sole markers for risk, because patients without TnT elevations may still exhibit a substantial risk of an adverse outcome. Neither marker is totally sensitive and specific in this regard [38]. The GUSTO trial evaluated the prognostic value of TnT based on the levels found in a single sample obtained at admission [3]. Of interest, even when TnT was negative, the risk of AMI in these patients was found to be as high as 63 %.

Thus this study shows that only a positive result is useful clinically, as a negative value does not necessarily exclude an evolving MI [39]. Lindahl et al. [31] showed that an elevated TnT identified patients at increased risk. However, even in the TnT negative patients there is still an incidence of cardiac death or MI of 4.3 %. Other authors reported an incidence of death or non-fatal MI of 17 % in TnT negative patients, and a need for revascularisation of 21 % [40]. The most obvious functional consequence of ischaemia is a rapidly manifested decrease in myocardial contractility. Loss of sarcomere contraction is observed within seconds of the onset of ischaemia in experimental models. With regional ischaemia, the risk area will become hypokinetic within a minute or so [41] and with global ischaemia complete arrest of the heart will occur. It is important to realise that reduced contractility occurs before the onset of tissue necrosis. However, it is recognised that impaired contractility in absence of necrosis may occur over prolonged periods in many clinical syndromes. Ultrastructural changes occur within 10 min. of the onset of ischaemia and, while it is difficult to give a precise sequence of events, the progression of morphological damage is critically time-dependent [42–45]. During ischaemia, the myocardium is mechanically quiescent but energy is still required to maintain homeostasis. Angina at rest is followed by a prolonged depression of contractile function, which may persist for up to 24 hours or even longer. This result is consistent with the concept that myocardial stunning does occur in unstable angina (UA) [46].

Recently it was shown that 2DE was able to identify patients who will have cardiac events. 2DE is more sensitive than ECG [15] and was able to discriminate between unstable angina with a high risk and low risk for adverse cardiac events [47]. In our previous studies we showed the utility of 2DE to identify patients with AMI without ST-elevation and high risk patients with unstable angina [48].

In general, the sensitivity and specificity of 2DE are best when it is used during or soon after an episode of pain. Small studies showed sensitivities and specificities of 86–92 % and 53–90 %, respectively [49]. A recent study showed that the combination of TnT determination plus 2DE in patients admitted to the ED with chest pain is a more powerful predictor of adverse cardiac events.

This study included patients with AMI, UA, stable angina, but no early angiography results were reported [50]. We found that the combination of the TnT test plus 2DE per-

Table 5. Kendall concordance coefficient (w) versus coronary artery angiography

	T-wave inversion		Non-diagnostic ECG	
	W	P	W	P
TnT +	0.7018	0.0066	0.6711	0.0061
2DE +	0.8831	< 0.0001	0.7879	< 0.0001
TnT + and 2DE	0.7018	0.0066	0.6404	0.02
TnT + plus 2DE	0.8831	< 0.0001	0.8183	< 0.0001

formed at entry on patients presenting with possible myocardial ischaemia identified those who had critical coronary stenosis. 2DE allowed us to identify a greater number of patients at risk with negative TnT test.

We divided the patients in 2 groups according to the ECG alterations at entry (T-wave inversion, non-diagnostic). In the group with T-wave inversion, we evidenced that 2DE and the combination 2DE + TnT showed a higher sensitivity and a negative predictive value. The group with non-diagnostic ECG was more complicated. It appears, in this group, that 2DE added significant incremental value either alone than combined with TnT to identify the patients at high risk. Mainly, we found that the combination, when negative, identified a large number of patients without coronary stenosis in all the groups, reducing in this way the number of false negative in patients with negative TnT test.

Our results suggest that the combination of TnT test and 2DE in patients presenting to EDs with chest pain either with T-wave inversion or without ECG changes is a useful tool to identify patients who can be discharged safely. We stress these results because we think that patients with positive results (on the TnT test) receive the immediate treatments and subsequent diagnostic procedures, while the patients with negative TnT test are the most important problems for admitting physicians because of the high incidence of false negatives. In fact, the TnT test identifies patients at high risk who are suffering from micronecrosis, but a greater number of patients with CAD do not experience micronecrosis because the ischaemia was less prolonged and was not able to cause cellular necrosis. This process, even if it does not cause necrosis can alter wall motion. We had difficulties to explain some of the results of our study. In fact, we observed patients with alterations of wall motion and positive TnT test but with non-critical stenosis. These patients probably experienced transient ischaemia because of platelet clot formation determined by endothelial dysfunction and rapid reperfusion, determined also by GP IIb/IIIa treatment. Another group of patients with negative combination showed successive CAD. We are not able to give an explanation, we hypothesised that these patients were suffering for not sufficiently prolonged ischaemia to determine TnT release, and possibly the ischaemia was confined to endocardium stratum only and not determining alteration of segmentary kinetic. Another hypothesis could be the localisation of alterations in myocardial area (high lateral or posterior) which is difficult to see by 2DE. Further studies are warranted to evaluate our data.

We think that our data are important because the combination of these tests can identify the high-risk (when positive) patients, and reduce the incidence of false negative, but most importantly, it allows to identify truly negative patients who can be discharged safely.

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