<https://helda.helsinki.fi>

Associations between ECG changes and echocardiographic findings in patients with acute non-ST elevation myocardial infarction

Tuohinen, Suvi Sirkku

2018

Tuohinen , S S , Rankinen , J , Skyttä , T , Huhtala , H , Virtanen , V , Kellokumpu-Lehtinen , P-L , Raatikainen , P & Nikus , K 2018 , ' Associations between ECG changes and echocardiographic findings in patients with acute non-ST elevation myocardial infarction ' , Journal of Electrocardiology , vol. 51 , no. 2 , pp. 188-194 . <https://doi.org/10.1016/j.jelectrocard.2017.11.007>

<http://hdl.handle.net/10138/301305>

<https://doi.org/10.1016/j.jelectrocard.2017.11.007>

publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Associations between ECG changes and echocardiographic findings in patients with acute non-ST elevation myocardial infarction☆

Suvi Sirkku Tuohinen, MD, PhD^{a,b,c,*}, Jani Rankinen, MS^{b,c}, Tanja Skyttä, MD, PhD^{b,d}, Heini Huhtala, MSc^e, Vesa Virtanen, MD, PhD^{b,c}, Pirkko-Liisa Kellokumpu-Lehtinen, MD, PhD^{b,d}, Pekka Raatikainen, MD, PhD^a, Kjell Nikus, MD, PhD^{b,c}

^a Heart and Lung Center, Helsinki University Central Hospital and Helsinki University

^b Faculty of Medicine and Life Sciences, University of Tampere, Finland

^c Heart Center, Tampere University Hospital, Finland

^d Department of Oncology, Tampere University Hospital, Finland

^e Faculty of Social Sciences, University of Tampere, Finland

ARTICLE INFO

Keywords:

Non-ST elevation infarction

ECG

Speckle tracking echocardiography

Integrated backscatter

ABSTRACT

Background: ST segment depression (STD) and T wave inversion (TWI) are typical electrocardiographic (ECG) findings in non-ST elevation myocardial infarction (NSTEMI). In ST elevation myocardial infarction, ST changes represent transmural ischemia. The pathophysiological mechanisms of the ECG changes in NSTEMI are unclear. **Purpose:** We studied the associations between ECG and the echocardiographic findings in NSTEMI patients.

Methods: Twenty patients with acute NSTEMI were recruited during their hospital stay. A comprehensive echocardiography study was performed. The findings were compared with blinded ECG analyses.

Results: Nine (45%) patients had STD, and 16 (85%) patients had TWI. In multivariable analysis, STD was independently associated with a lower global early diastolic strain rate ($\beta = -5.061$, $p = 0.033$). TWI was independently associated with lower circumferential strain ($\beta = 0.132$, $p = 0.032$).

Conclusions: The typical ECG changes in NSTEMI patients were associated with subtle echocardiographic changes. STD was related to changes in diastolic function, and TWI was associated with systolic deterioration.

© 2017 Elsevier Inc. All rights reserved.

Introduction

In ST elevation myocardial infarction (STEMI), acute coronary occlusion causes transmural myocardial ischemia, which is expressed as ST elevations and prominent positive T waves on the electrocardiogram (ECG). The location of the ST elevations on the ECG depends on the ischemic myocardial region [1]. On the other hand, non-ST elevation myocardial infarction (NSTEMI) is a heterogeneous clinical condition with a variable pathophysiological background. ST depression (STD) and T wave inversion (TWI) are the typical ECG changes in NSTEMI patients. STD is most often located in the lateral precordial leads, V4–V6, independent of the coronary anatomy [2–4]. “Wellens’ syndrome” – TWI in precordial leads V1–V3/V4 caused by a lesion in the left anterior descending coronary artery (LAD) – is an example of the association between the location of TWI on the ECG and the culprit artery in acute coronary syndrome [4].

Echocardiography has a central role in the diagnosis and risk stratification of acute myocardial infarction (MI) patients [5]. Newer techniques, such as tissue Doppler imaging and speckle tracking echocardiography, have emerged as valuable diagnostic and prognostic tools in patients with acute coronary syndrome [6]. Their roles in the clinical evaluation of NSTEMI patients are being explored.

The goal of our study was to evaluate the relationships between ECG changes and concurrent echocardiographic findings in patients with acute NSTEMI. This comparison may shed some light on the mechanisms behind these ECG changes, which in turn potentially could improve risk stratification in acute coronary syndrome patients. We hypothesize that STD and TWI may differ with respect to their association with echocardiographic systolic and diastolic functional parameters.

Materials and methods

Patient selection

Patients were recruited at the Heart Center Tampere University Hospital from April 2012 to June 2015. Twenty NSTEMI patients without

☆ Conflict of interest: None to declare.

* Corresponding author at: Heart and Lung Center, Helsinki University Central Hospital and Helsinki University, PO Box 340, 00029 Helsinki, Finland.

E-mail addresses: suvi.tuohinen@finnet.fi, suvi.tuohinen@hus.fi (S.S. Tuohinen).

a history of cardiac disease were recruited after coronary angiography. The exclusion criteria were significant valvular stenosis or regurgitation (grade 2 or higher), prior MI, non-sinus rhythm, the presence of a pacemaker, wide QRS complex (N120 ms), and severe lung disease or other significant pathology, such as severe infection or pericardial effusion. The study protocol was approved by the local ethical committee (R11149) and each patient signed an informed consent form before enrollment in the study.

Cardiac examinations

All patients underwent coronary angiography during their hospital stay and repeated analyses of biomarkers and 12-lead ECG recordings were conducted according to the normal hospital protocol.

A 12-lead ECG was routinely recorded upon arrival to the hospital and repeated at least once during the hospital stay. The ECG closest to the time of the echocardiographic study was used in the analysis. A manual analysis of the ECG was performed with a magnifying lens by two authors (JR and KN) blinded to the clinical and echocardiographic data. The data were analyzed separately for three anatomic territories corresponding to the coronary artery distribution: anterior territory leads V1–V4 (LAD territory), inferior territory leads II, III and aVF (right coronary artery territory, RCA), and lateral territory leads I, aVL and V5–V6 (left circumflex artery territory, LCX), please see Fig. 1. The cut-off value for STD was 0.05 mV at the J point. The corresponding value for TWI was 0.1 mV. Both STD and TWI had to be present in at least two contiguous leads (Fig. 2). Pathological Q waves were defined according to current guidelines [7].

Thorough echocardiography was performed within one (0 to 2) day after coronary angiography. Invasive procedures were performed according to the current national and international guidelines and this

was also the case for anti-thrombotic and anti-ischemia medical therapy [8]. All echocardiographic examinations were performed with a commercially available cardiac ultrasound machine (Philips iE33 ultrasound system, Bothell, Washington, USA) and a 1–5 MHz matrix-array X5-1 transducer by the same cardiologist (SST). All imaging was acquired at rest with the patients in the left lateral decubitus position. Doppler recordings were acquired at end-expiration. A simultaneous superimposed ECG was used throughout the studies. The images were stored in an external hard drive for off-line analysis (Philips Qlab, Bothell, Washington, USA). For the wall motion score analysis, the left ventricle was divided into 17 segments [9]. Each segment received a grade as follows: 1 - normal, 2 - hypokinesia, 3 - akinesia and 4 - dyskinesia. The total wall motion score was calculated by adding the score of each segment and the wall motion score index was obtained by dividing the total wall motion score by the number of left ventricular segments.

The analysis to compare the ECG and echocardiographic results was conducted in two ways. First, echocardiographic parameters reflecting global changes were compared with the presence of STD or TWI. Second, the left ventricle was divided into the three segments corresponding to the regions perfused by the LAD, RCA and LCX. The regional results reflecting these segments were compared with corresponding changes in the ECG (Fig. 1).

Statistical analysis

Data are reported as means and standard deviations for normally distributed variables and as medians with ranges for other continuous variables. Differences in baseline characteristics between the groups were tested with the independent samples Student's t-test for continuous variables and with Fisher's exact test for categorical variables. Differences between the groups were analyzed with independent

Fig. 1. Regional analysis. A 17-segment model of the left ventricle is presented on the right. The colors represent the segment distribution for the speckle tracking analysis. The integrated backscatter analysis is represented on the left with anteroseptal (red) values reflecting the LAD artery distribution area and posterior (yellow) values reflecting the inferior territory (the RCA distribution area). LAD = left anterior descending; RCA = right coronary artery; LCX = left circumflex; OM = obtuse marginal; LD = left diagonal; IM = intermediate branch.

Fig. 2. ECG changes in two NSTEMI patients. Patient A (left side) had a 95% stenosis in the right coronary artery without other concomitant lesions. A percutaneous intervention for the stenosed vessel was performed prior this ECG recording and echocardiography. ST depressions and T-wave inversions are present in leads II, III, aVF and 6. In patient B, there are T-wave inversions in leads aVL and V1–V5 and angiography showed 90% stenosis in the left anterior descending coronary artery with less severe lesions in the right posterior descending and left obtuse marginal branches. He had coronary artery by-pass grafting within a week after this recording. The speed of the ECG recordings is 50 mm/s according to national standard.

samples t-tests for normally distributed variables or with the independent samples Mann Whitney U test for variables with skewed distribution and categorical variables were analyzed with the χ^2 /Fishers exact test. Associations between variables were calculated with Spearman correlations. A regression analysis was used to test univariate associations and a linear forward regression analysis was used to test multivariable associations. The tested variables are shown in Tables 3 and 4. Statistical analyses were carried out with IBM SPSS Statistics for Windows, Version 23.

Results

General characteristics

The patient population had a male predominance (80%) with a mean age of 63 ± 9 years. For other baseline characteristics, please see Table 1. The patient characteristics showed no significant differences across different ECG findings.

The median duration of angina pectoris prior to hospitalization was 2.5 days (0 to 21 days) and coronary angiography was performed within 1 day (0 to 2 days) of hospital admission. The echocardiographic examination was performed 1 day (0 to 6 days) after angiography. Coronary angiography revealed one-vessel disease in eight (40%) patients, two-vessel disease in seven (35%) patients and three-vessel disease in five (25%) patients. None of the patients had left main coronary artery involvement. Three patients had a total occlusion (one proximal LCX, one mid-RCA and one distal RCA); none of these patients were considered “STEMI equivalent” based on the ECG findings. At the time of echocardiography, 14 (70%) patients were treated with percutaneous coronary artery intervention (PCI) with stenting for their culprit lesion. The remaining patients had received medical treatment and four (20%) patients were scheduled to undergo coronary artery by-pass surgery later on.

Regarding myocardial ischemia after invasive evaluations and therapy, 16 (27%) of 60 segments had been treated successfully with PCI, 21

(35%) segments had normal coronary flow, and 23 (38%) segments were still supplied by coronary arteries with significant stenosis (diameter of stenosis $\geq 50\%$). All patients were stable at the time of echocardiography and were either transferred to a local hospital or discharged from our hospital within 4 (1 to 20) days after hospital admission.

Table 1
Characteristics of the study population.

	The entire group	
	n = 20	
	Mean/median	SD/(Q ₁ , Q ₃)
Age (years)	63.0	9.3
Systolic blood pressure (mm Hg)	131	(124, 142)
Diastolic blood pressure (mm Hg)	81	(68, 89)
BMI (kg/m ²)	27.6	(24.5, 30.0)
max hsTnt (ng/l)	189	(74, 727)
n		%
Sex (male)	16	80
Hypertension	9	45
Diabetes	4	20
High cholesterol	13	65
Familial predisposition for coronary artery disease	12	60
Smoking		
Current	6	30
Previous	3	15
Medical treatment at the time of echocardiography		
Beta blockers	14	70
Calcium channel blockers	3	15
ACE inhibitors/ARB	13	65
Diuretics	1	5
Acetylsalicylic acid	18	90
Clopidogrel	11	55
Statins	13	65
Diabetes medications	1	5

BMI, body mass index; hsTnt, high-sensitivity troponin T; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

ECG findings

All patients had sinus rhythm with an average heart rate of 69 ± 16 bpm. No conduction defects were observed. The median QRS-complex width was 93 [83, 104] ms. One patient had a pathological Q wave in the LAD territory without concurrent STD or TWI. Nine (45%) patients had STD and TWI was present in 16 (80%) patients. Three (15%) patients had neither STD nor TWI in their ECGs at the time of echocardiography. At the regional level, STD was observed in 17/60 (28%) of the segments and TWI was observed in 28/60 (47%) of the segments. In 12/60 (12%) segments, both STD and TWI were present and in 27/60 (45%) segments, no abnormal findings were observed in the ST segments or the T waves.

Time delays from hospital arrival or the time from symptom onset to treatment were not different according to the presence or absence of STD or TWI. TWI was more prevalent in segments with ischemia (coronary stenosis) according to coronary angiography ($p = 0.058$). The positive predictive values (PPV) of TWI and STD for segments with ischemia were 79% and 82%, the negative predictive values (NPV) were 47% and 42%, the sensitivity scores were 56% and 36% and the specificity scores were 71% and 86%, respectively. In the absence of both STD and TWI, the existence of significantly stenosed coronary arteries was significantly less prevalent ($p = 0.017$). The PPV to predict a non-ischemic segment was 52%, the NPV was 79%, the sensitivity was 41% and the specificity was 67%.

Echocardiographic findings

The echocardiography findings are presented in Table 2. In general, the left ventricle exhibited normal size without overt systolic or diastolic dysfunction. Half of the patients showed no regional changes in contractility and the rest showed hypokinesia in 1.6 ± 1.3 segments.

Findings in echocardiography in patients with STD

Compared to patients without STD, patients with STD had longer isovolumetric relaxation time (IVRT) (142 ± 19 ms vs 114 ± 25 ms,

$p = 0.007$), lower global early diastolic velocity (e') in the speckle tracking echocardiography analysis ($0.83/s$ [$0.77, 1.02$] vs $1.08/s$ [$0.99, 1.21$], $p = 0.006$) and lower values of posterior cyclic variation in the integrated backscatter (pCVIBS) analysis (8.9 ± 1.9 dB vs 12.3 ± 2.9 dB, $p = 0.043$). STD showed correlations with diabetes ($r = \checkmark 0.452$, $p = 0.045$), smoking ($r = 0.596$, $p = 0.006$), pCVIBS ($r = \checkmark 0.462$, $p = 0.040$), e' ($\checkmark 0.619$, $p = 0.004$), and global circumferential strain (GCS) in the speckle tracking echocardiography analysis ($r = \checkmark 0.457$, $p = 0.049$) and with IVRT ($r = 0.629$, $p = 0.003$). The univariate and multivariable analyses of the factors associated with STD are presented in Table 3. Globally, IVRT and e' were independently associated with the presence of STD. Regional changes showed independent associations with e' and STD.

Findings in echocardiography in patients with TWI

Compared to patients without TWI, patients with TWI had lower left ventricular ejection fraction (LVEF), ($57 \pm 6\%$ vs $71 \pm 4\%$, $p = 0.008$) and lower global systolic strain rate (s') in the speckle tracking echocardiography analysis ($\checkmark 1.09/s$ [$\checkmark 1.22, \checkmark 0.98$] vs $\checkmark 1.31/s$ [$\checkmark 1.67, \checkmark 1.15$], $p = 0.050$). TWI showed correlations with smoking ($r = 0.452$, $p = 0.045$), s' ($r = \checkmark 0.455$, $p = 0.044$) and LVEF ($r = \checkmark 0.586$, $p = 0.007$). The results of the univariate and multivariable analyses of TWI are presented in Table 4. Globally, TWI was independently associated with s' and hypertension. The regional changes were independently associated with circumferential strain. Patients with TWI had lower circumferential strain ($\checkmark 26.8 \pm 4.4\%$ vs $\checkmark 29.7 \pm 4.1\%$, $p = 0.013$).

Cardiac biomarkers

Cardiac biomarkers were elevated. Upon hospital arrival, the median (Q_1, Q_3) of the high-sensitivity troponin T (hsTnt) was 117 ng/l (43, 196) (normal ≤ 15 ng/l) with a maximum value of 189 ng/l (74, 727) during the hospital stay. Pro-B-type natriuretic peptide (ProBNP) was 1003 ng/l (567, 1464), hemoglobin was 140 ng/l (136, 151), total cholesterol was 4.7 mmol/l (4.1, 5.7), LDL was 3.2 mmol/l (2.5, 4.0) and

Table 2
Echocardiographic results of the study population.

	All patients		Patients with STD			Patients with TWI		
	n = 20		n = 9			n = 16		
	Mean/median	SD/(Q ₁ , Q ₃)	Mean/median	SD/(Q ₁ , Q ₃)	p	Mean/median	SD/(Q ₁ , Q ₃)	p
Structures								
LVEDD	49.6	4.0	50.3	3.8	0.528	50.2	3.2	0.329
LVEDS	33.6	4.3	34.2	3.6	0.628	34.5	3.2	0.051
IVS	11.3	(10.8, 11.8)	11.5	(10.9, 12.0)	0.295	11.1	(10.8, 11.8)	0.682
PW	11.4	(10.7, 12.4)	11.4	(10.0, 12.2)	0.710	11.6	(10.5, 12.4)	0.617
cIBS	$\checkmark 16.5$	4.1	$\checkmark 15.4$	4.8	0.884	$\checkmark 16.1$	4.0	0.871
Diastolic function								
Mitral E-wave	72	21	67	21	0.180	70	20	0.098
Mitral ea-ratio	0.93	(0.85, 1.39)	0.90	(0.81, 0.96)	0.238	0.93	(0.86, 1.43)	0.655
IVRT	127	26	142	19	0.007	129	28	0.277
STE global e'	1.01	(0.86, 1.13)	0.83	(0.77, 1.02)	0.006	1.00	(0.79, 1.14)	0.617
STE global a'	1.15	(0.89, 1.33)	1.27	(1.09, 1.48)	0.331	1.10	(0.94, 1.30)	0.211
Systolic function								
LVEF	59	8	58	10	0.328	57	6	0.008
GLS	$\checkmark 15.4$	2.4	$\checkmark 14.8$	2.6	0.136	$\checkmark 15.2$	2.2	0.524
GCS	$\checkmark 28.4$	4.3	$\checkmark 27.3$	3.6	0.123	$\checkmark 27.9$	4.6	0.322
STE global s'	$\checkmark 1.10$	($\checkmark 1.21, \checkmark 1.00$)	$\checkmark 1.12$	($\checkmark 1.18, \checkmark 0.99$)	0.824	$\checkmark 1.09$	($\checkmark 1.22, \checkmark 0.98$)	0.050
sCVIBS	8.5	2.7	7.9	1.7	0.308	8.6	2.9	0.899
pCVIBS	10.7	3.0	8.9	1.9	0.043	10.8	3.0	0.835
WMSI	1.00	(1.00, 1.03)	1.00	(1.00, 1.06)	0.882	1.01	(1.00, 1.03)	0.750

LVEDD and LVEDS, left ventricular end-diastolic and end-systolic diameters; IVS and PW, interventricular and posterior wall thickness; cIBS, calibrated integrated backscatter derived from the parasternal long axis view from the interventricular septum; Mitral E-wave, mitral inflow E-wave velocity; Mitral ea-ratio, ratio between mitral inflow E and a waves; IVRT, isovolumetric relaxation time; STE, speckle tracking echocardiography; LVEF, left ventricular ejection fraction; GLS and GCS, global longitudinal and circumferential strain in STE; sCVIBS and pCVIBS, cyclic variation of the integrated backscatter derived from the septum and posterior wall; WMSI, wall motion score index. The p-value represents the difference between patients with and without changes in STD and TWI.

Bold text indicates statistically significant changes with $p \leq 0.05$ and text with italics indicates p-value between 0.05–0.10.

Table 3
Factors associated with STD

	Univariate analysis			Multivariable analysis		
	β	SE(β)	p	β	SE(β)	p
Global ST depression						
WMSI	15.044	15.763	0.340			0.845
GLS (%)	0.325	0.219	0.138			0.753
STE systolic strain rate (1/s)	$\hat{S}$ 1.436	2.341	0.540			0.985
STE early diastolic strain rate (1/s)	$\hat{S}$ 9.642	4.316	0.025	$\hat{S}$ 1.276	0.435	0.010
GSC (%)	0.188	0.125	0.133			0.826
Mitral inflow	$\hat{S}$ 0.036	0.027	0.189			0.561
E-wave (cm/s)						
IVRT (ms)	0.061	0.029	0.032	0.007	0.003	0.029
LVEF (%)	$\hat{S}$ 0.071	0.065	0.275			0.888
CVIBS (dB)	$\hat{S}$ 0.254	0.258	0.324			0.958
Sex	0.251	1.120	0.822			0.961
Hypertension	0.875	0.931	0.347			0.959
Diabetes	21.454	20096.487	0.999			0.746
High cholesterol	$\hat{S}$ 0.134	0.945	0.888			0.987
Age	0.012	0.050	0.805			0.968
Smoking	$\hat{S}$ 1.281	1.030	0.214			0.869
Regional ST depression						
WMSI	3.296	6.059	0.586			0.584
STE longitudinal strain (%)	0.057	0.04	0.158			0.771
STE systolic strain rate (1/s)	$\hat{S}$ 0.355	0.960	0.727			0.894
STE early diastolic strain rate (1/s)	$\hat{S}$ 5.498	1.791	0.002	$\hat{S}$ 5.061	2.376	0.033
STE late diastolic strain rate (1/s)	0.864	0.792	0.275			0.274
STE circumferential strain (%)	0.130	0.056	0.020			0.729
CVIBS (dB)	$\hat{S}$ 0.267	0.182	0.142			0.103
cIBS (dB)	$\hat{S}$ 0.056	0.041	0.177			0.394
Sex	0.762	0.674	0.258	2.964	1.756	0.091
Hypertension	1.318	0.648	0.042	2.992	1.554	0.054
Diabetes	20.602	11602.713	0.999			0.239
High cholesterol	0.018	0.600	0.976			0.597
Age	0.017	0.032	0.593			0.504
Smoking	$\hat{S}$ 0.711	0.604	0.239			0.290

STD, ST-level depression on ECG; WMSI, wall motion score index; GLS and GCS, global longitudinal and circumferential strain; STE, speckle tracking echocardiography; IVRT, isovolumetric relaxation time; LVEF, left ventricular ejection fraction; CVIBS, cyclic variation of the integrated backscatter; cIBS, calibrated integrated backscatter. Bold text indicates statistically significant changes with $p < 0.05$ and text with italics indicates p -value between 0.05–0.10.

creatinine was 72 $\mu\text{mol/l}$ (62, 83). We found no associations between biomarker values and ECG changes.

Discussion

In NSTEMI patients, TWIs were associated with changes in systolic function and their locations corresponded with the anatomic distribution of myocardial ischemia. On the other hand, the distribution of STD in the 12 ECG leads did not correlate with the locations of wall motion abnormalities in echocardiography. STD was associated with global and regional changes in diastolic function.

Clinical implications of our findings

Tissue Doppler imaging and speckle tracking echocardiography have revolutionized the quantitative evaluation of myocardial function. Our study, which utilized these new echocardiographic techniques, provides some new insight into the possible mechanisms behind STD and TWI on the ECG. It is intriguing that STD was associated with diastolic parameter changes and TWI with systolic parameter changes. In NSTEMI, it is evident that these ECG changes are caused by different mechanisms, at least to some extent. First, STD is a robust prognostic factor in non-

Table 4
Factors associated with TWI.

	Univariate analysis			Multivariable analysis		
	β	SE(β)	p	β	SE(β)	p
Global T-wave inversion						
WMSI						0.391
GLS (%)	0.168	0.252	0.504			0.918
STE systolic strain rate (1/s)	7.517	4.215	0.075	1.002	0.314	0.006
STE early diastolic strain rate (1/s)	$\hat{S}$ 1.928	2.865	0.501			0.595
GSC (%)	0.159	0.161	0.324			0.422
Mitral inflow E-wave (cm/s)	$\hat{S}$ 0.044	0.028	0.116			0.880
IVRT (ms)	0.028	0.025	0.273			0.486
LVEF (%)	$\hat{S}$ 0.449	0.240	0.062			0.314
CVIBS (dB)	9.050	21.053	0.667			0.498
Sex	$\hat{S}$ 0.368	1.320	0.781			0.167
Hypertension	1.609	1.265	0.203	$\hat{S}$ 0.311	0.127	0.026
Diabetes	0.368	1.320	0.781			0.851
High cholesterol	$\hat{S}$ 0.788	1.136	0.488			0.429
Age	$\hat{S}$ 0.094	0.075	0.211			0.958
Smoking	$\hat{S}$ 20.287	16408.713	0.999			0.648
Regional T-wave inversion						
WMSI	11.236	6.981	0.108			0.207
STE longitudinal strain (%)	0.060	0.037	0.103			0.160
STE systolic strain rate (1/s)	1.928	1.085	0.076			0.136
STE early diastolic strain rate (1/s)	$\hat{S}$ 1.651	1.142	0.148			0.344
STE late diastolic strain rate (1/s)	$\hat{S}$ 0.977	0.748	0.191			0.444
STE circumferential strain (%)	0.1340	0.051	0.007	0.132	0.061	0.032
CVIBS (dB)	$\hat{S}$ 0.090	0.116	0.440			0.261
cIBS (dB)	$\hat{S}$ 0.032	0.036	0.380			0.394
Sex	$\hat{S}$ 0.253	0.635	0.698			0.988
Hypertension	0.713	0.530	0.179			0.273
Diabetes	$\hat{S}$ 0.167	0.646	0.796			0.262
High cholesterol	0.059	0.542	0.914			0.989
Age	$\hat{S}$ 0.041	0.030	0.171			0.239
Smoking	$\hat{S}$ 0.838	0.577	0.146			0.313

TWI, T-wave inversion on ECG; WMSI, wall motion score index; GLS and GCS, global longitudinal and circumferential strain; STE, speckle tracking echocardiography; IVRT, isovolumetric relaxation time; LVEF, left ventricular ejection fraction; CVIBS, cyclic variation of the integrated backscatter; cIBS, calibrated integrated backscatter. Bold text indicates statistically significant changes with $p < 0.05$ and text with italics indicates p -value between 0.05–0.10.

ST elevation acute coronary syndrome (NSTEMI and unstable angina combined), but the prognostic significance of TWI is controversial [2, 10]. Both the presence and the magnitude of STD and the number of leads with these changes have prognostic impact [2, 11]. Second, STD is a typical ECG finding during angina pectoris symptoms, while isolated TWI almost never appears during angina pectoris symptoms. Instead, recurrent ischemic symptoms cause “pseudo-normalization” or ST elevations in patients with TWI [12]. Third, TWI, but not STD, tends to be located in the leads that correspond to an ischemic/infarcted region [2, 13].

There is clearly a large knowledge gap regarding the possible pathophysiological mechanisms of STD and TWI in patients with NSTEMI. STD is the hallmark of subendocardial ischemia in patients with stable angina pectoris [4]. Subendocardial MI is a known condition in cardiac imaging, but its association with ECG changes in this context has not been studied in detail [4]. The exploration of the pathophysiological mechanisms behind STD is challenging. In animal experiments, the induction of subendocardial ischemia resulted in a significant increase in the end-diastolic pressure of the left ventricle and loss of left ventricular chamber compliance, indicating diastolic dysfunction [14, 15]. The fact that STD in our patients was associated with changes in diastolic function parameters is consistent with the experimental hemodynamic data.

The etiology of TWI in NSTEMI is probably multifactorial. TWI in STEMI patients has been associated with improved outcome related to an open infarct-related artery and restored blood flow [16]. However, TWI has also been associated with non-patency of the culprit artery and worse short-term outcome in late-presenting patients [17]. Interestingly, the results of a recent study with a large number of patients showed that 20% of the patients presenting with NSTEMI and single-vessel disease had a totally occluded culprit artery [18]. Additionally, cardiac magnetic resonance imaging (CMR) data have shown that approximately 25% of NSTEMI patient had transmural infarction [19]. Therefore, it can be speculated that MI patients presenting late may have passed the initial stage showing ST elevation and show only “post-ischemic” TWI on the ECG [12]. It is possible that the rapid restoration of normal myocardial function is not achieved in these patients with therapeutic interventions and they may instead develop varying degrees of myocardial edema and stunning [20]. Indeed, in a small study on a sub-type of NSTEMI with TWI – “Wellens’ syndrome” – the patients had myocardial edema on cardiac CMR [21]. In addition, repolarization abnormalities on the ECG and myocardial edema had similar time courses. Our study showed an association between TWI and echocardiographic markers of systolic dysfunction on speckle tracking echocardiography analysis. Interestingly, regional echocardiographic changes correlated with the ischemic regions on the ECG.

Tissue Doppler and speckle tracking echocardiography - comparison with previous studies

Data on the clinical roles of the new echocardiographic modalities in coronary artery disease are emerging. Several studies and a recent meta-analysis indicate that speckle tracking echocardiography derived strain is associated with global left ventricular function and has prognostic value in patients with acute STEMI [22,23]. However, data on NSTEMI patients are limited. We are not aware of any previous study that has investigated ECG and echocardiography parameters utilizing newer imaging methods. Considering the high rate of NSTEMI patients with a totally occluded culprit artery and the limitations of the ECG to identify this subgroup, it is important to identify these individuals with other diagnostic modalities such as echocardiography [18]. Study results in 40 NSTEMI patients with preserved left ventricular function indicated that speckle tracking echocardiography may be a more sensitive discriminator of left ventricular dyssynchrony than tissue Doppler imaging [24]. In another study including 111 patients with suspected NSTEMI who received echocardiography within 1 h (median value; interquartile range 0.5–4 h) of admittance, 61% had a clinical diagnosis of NSTEMI, 16% had a diagnosis of unstable angina, and 23% had non-coronary chest pain [25]. Territorial systolic strain, measured by averaging all segmental peak systolic strain values in each territory in the 16-segment left ventricular model, proved to be the most reliable method to identify acute total occlusion. A territorial circumferential strain value $\leq 10\%$ had 90% sensitivity and 88% specificity for the identification of a totally occluded culprit artery. Symmetrical TWI was present in 33% and 31% of the patients with an occluded and a non-occluded culprit artery, respectively. Our patients had a higher frequency of TWI, but we did not restrict the definition of TWI to symmetrical T waves and in our study, all patients had NSTEMI. In our study, patients with TWI had lower circumferential strain.

Limitations of our study

Our study has clear limitations. The patient population was small. Therefore, all speculations regarding pathophysiological mechanisms should be considered hypothetical, especially since CMR was not part of the protocol. Additionally, the limited number of patients made it impractical to introduce patients with both STD and TWI as a third group in the statistical analyses.

Conclusion

In NSTEMI patients with well-preserved global left ventricular systolic function, subtle changes in myocardial imaging were found. STD was associated with changes in diastolic function, and TWI was associated with systolic deterioration. The findings are consistent with the proposed pathophysiological mechanisms behind these ECG changes.

Disclosure of interest

The authors state no conflict of interest related to the study.

Funding

This study was supported by the Paavo and Eila Salonen Legacy, Ida Montin Fund, The Finnish Medical Foundation, The Finnish Cultural Foundation, Pirkanmaa Regional Fund, The Finnish Foundation for Cardiovascular Research, Finnish Society of Oncology, Pirkanmaa Cancer Society, Finnish-Norwegian Medical Foundation, The Pirkanmaa Hospital District, and The Aarne and Aili Turunen Foundation.

Acknowledgements

The authors thank the research nurses, Virpi Räsänen, Hanna Näppilä and Kati Helleharju, for their expert assistance during the study.

References

- [1] Gregg RE, Babaeizadeh S. Detection of culprit coronary lesion location in pre-hospital 12-lead ECG. *J Electrocardiol* 2014;47(6):890–4.
- [2] Atar S, Fu Y, Wagner GS, Rosanio S, Barbagelata A, Birnbaum Y. Usefulness of ST depression with T-wave inversion in leads V(4) to V(6) for predicting one-year mortality in non-ST-elevation acute coronary syndrome (from the Electrocardiographic Analysis of the Global Use of Strategies to Open Occluded Coronary Arteries IIB Trial). *Am J Cardiol* 2007;99(7):934–8.
- [3] Birnbaum Y, Nikus K, Kligfield P, Fiol M, Barrabes JA, Sionis A, et al. The role of the ECG in diagnosis, risk estimation, and catheterization laboratory activation in patients with acute coronary syndromes: a consensus document. *Ann Noninvasive Electrocardiol* 2014;19(5):412–25.
- [4] Ishida M, Kato S, Sakuma H. Cardiac MRI in ischemic heart disease. *Circ J* 2009;73(9):1577–88.
- [5] Leischik R, Dworak B, Sanchis-Gomar F, Lucia A, Buck T, Erbel R. Echocardiographic assessment of myocardial ischemia. *Ann Transl Med* 2016;4(13):259.
- [6] Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? *Eur Heart J* 2016;37(15):1196–207.
- [7] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126(16):2020–35.
- [8] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37(3):267–315.
- [9] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18(12):1440–63.
- [10] Mueller C, Neumann FJ, Perach W, Perruchoud AP, Buettner HJ. Prognostic value of the admission electrocardiogram in patients with unstable angina/non-ST-segment elevation myocardial infarction treated with very early revascularization. *Am J Med* 2004;117(3):145–50.
- [11] Barrabes JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Prognostic significance of ST segment depression in lateral leads I, aVL, V5 and V6 on the admission electrocardiogram in patients with a first acute myocardial infarction without ST segment elevation. *J Am Coll Cardiol* 2000;35(7):1813–9.
- [12] Nikus K, Pahlm O, Wagner G, Birnbaum Y, Cinca J, Clemmensen P, et al. Electrocardiographic classification of acute coronary syndromes: a review by a committee of the International Society for Holter and non-invasive electrocardiology. *J Electrocardiol* 2010;43(2):91–103.
- [13] de Luna AB, Zareba W, Fiol M, Nikus K, Birnbaum Y, Baranowski R, et al. Negative T wave in ischemic heart disease: a consensus article. *Ann Noninvasive Electrocardiol* 2014;19(5):426–41.
- [14] Palacios I, Johnson RA, Newell JB, Powell Jr WJ. Left ventricular end-diastolic pressure volume relationships with experimental acute global ischemia. *Circulation* 1976;53(3):428–36.

- [15] Guyton RA, McClenathan JH, Newman GE, Michaelis LL. Significance of subendocardial S-T segment elevation caused by coronary stenosis in the dog. Epicardial S-T segment depression, local ischemia and subsequent necrosis. *Am J Cardiol* 1977;40(3):373–80.
- [16] Doevendans PA, Gorgels AP, van der Zee R, Partouns J, Bar FW, Wellens HJ. Electrocardiographic diagnosis of reperfusion during thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1995;75(17):1206–10.
- [17] Herz I, Birnbaum Y, Zlotikamien B, Strasberg B, Sclarovsky S, Chetrit A, et al. The prognostic implications of negative T waves in the leads with ST segment elevation on admission in acute myocardial infarction. *Cardiology* 1999;92(2):121–7.
- [18] Warren J, Mehran R, Yu J, Xu K, Bertrand ME, Cox DA, et al. Incidence and impact of totally occluded culprit coronary arteries in patients presenting with non-ST-segment elevation myocardial infarction. *Am J Cardiol* 2015;115(4):428–33.
- [19] Sarafoff N, Schuster T, Vochem R, Fichtner S, Martinoff S, Schwaiger M, et al. Association of ST-elevation and non-ST-elevation presentation on ECG with transmural and size of myocardial infarction as assessed by contrast-enhanced magnetic resonance imaging. *J Electrocardiol* 2013;46(2):100–6.
- [20] Mewton N, Bonnefoy E, Revel D, Ovize M, Kirkorian G, Croisille P. Presence and extent of cardiac magnetic resonance microvascular obstruction in reperfused non-ST-elevated myocardial infarction and correlation with infarct size and myocardial enzyme release. *Cardiology* 2009;113(1):50–8.
- [21] Migliore F, Zorzi A, Marra MP, Basso C, Corbetti F, De Lazzari M, et al. Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction. *Heart Rhythm* 2011;8(10):1629–34.
- [22] Orii M, Hirata K, Tanimoto T, Shiono Y, Shimamura K, Ishibashi K, et al. Two-dimensional speckle tracking echocardiography for the prediction of reversible myocardial dysfunction after acute myocardial infarction: comparison with magnetic resonance imaging. *Echocardiography* 2015;32(5):768–78.
- [23] Shetye A, Nazir SA, Squire IB, McCann GP. Global myocardial strain assessment by different imaging modalities to predict outcomes after ST-elevation myocardial infarction: a systematic review. *World J Cardiol* 2015;7(12):948–60.
- [24] Ng AC, Tran da T, Newman M, Allman C, Vidaic J, Leung DY. Comparison of left ventricular dyssynchrony by two-dimensional speckle tracking versus tissue Doppler imaging in patients with non-ST-elevation myocardial infarction and preserved left ventricular systolic function. *Am J Cardiol* 2008;102(9):1146–50.
- [25] Grenne B, Eek C, Sjöli B, Dahlslett T, Uchto M, Hol PK, et al. Acute coronary occlusion in non-ST-elevation acute coronary syndrome: outcome and early identification by strain echocardiography. *Heart* 2010;96(19):1550–6.