ORIGINAL ARTICLE

Variations of electrocardiographic parameters during hospitalization predict long-term outcomes in patients with non-ST-segment elevation myocardial infarction

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Abstract

Background: Electrocardiogram is an essential modality for diagnosis and early risk stratification for patients with acute coronary syndrome (ACS), but its long-term prognostic value has not been well studied. This study tried to investigate the long-term prognostic value of variations of ECG parameters at admission and discharge in patients with non-ST-segment elevation myocardial infarction (NSTEMI).

Methods: A total of 170 NSTEMI patients were recruited consecutively from 2013 to 2014 in West China Hospital of Sichuan University. All subjects' ECGs at admission and discharge were reviewed. Follow-up was performed, and the survival difference between groups was analyzed.

Results: Comparing with at admission, NSTEMI patients at discharge with a wider P wave (19.4% vs. 8.1%, $p = 0.047$), with new-onset PtfV1 positive (31.2% vs. 8.1%, 11.5%, 13.3%, $p = 0.147$) and with a greater number of leads showing ST depression (21.9% vs. 10.3%, $p = 0.037$) were prone to MACEs during long-term follow-up. The independent risk factors for the primary endpoints determined using a multivariate cox regression were new-onset PtfV1 positive during hospitalization (HR = 4.705, 95% CI = 1.457–15.197, $p = 0.010$) and prolonged QRS duration at discharge comparing to admission (HR = 2.536, 95% CI = 1.057–6.083, $p = 0.030$), besides diabetes mellitus, stage 3 hypertension, and multiple vessel lesions.

Conclusion: Discharge ECG with new-onset PtfV1 positive and prolonged QRS duration were independent risk factors for recurrence of MACEs in NSTEMI patients. The differences of ECG parameters between at admission and discharge, including P-wave duration, number of leads with ST-segment depression, carried long-term prognostic information for NSTEMI patients.

1 | INTRODUCTION

Acute non-ST-segment elevation myocardial infarction (NSTEMI) is in the spectrum of acute coronary diseases (ACS) and often life-threatening. Several methods were developed to assess the early and late risk. As a noninvasive, convenient, and cost-effective approach, ECG was done repeatedly on ACS patients during hospitalization to monitor disease and evaluate the risk. Several

electrocardiographic parameters have been widely considered as predictive of risk. According to ESC guidelines for the management of acute coronary syndromes published in 2015, the number of leads showing ST depression and the magnitude of it, indicative of the range and severity of ischemic attack, suggests adverse prognosis in NSTEMI patients (Roffi et al., 2016). However, the prognostic ability of ECG seems not limited to that.

P wave is an excitement of atria, and abnormalities of it are known to be associated with chamber dilatation, muscular hypertrophy, intra-atrial conduction delay, and elevated pressure. Especially, P-wave duration ≥ 110 ms irrespective of morphology, which indicates interatrial block (IAB), is a risk factor for congestive heart failure (Goyal & Spodick, 2001). As reported in prior publications, reversion of P-wave duration was correlated to improvement of clinical and laboratory results (Proietti, Mafri, & Spodick, 2012) and had short-term prognostic ability in patients with myocardial infarction (Shturman, Bickel, & Atar, 2012). In general, P wave could be divided into initial and terminal portions when diphasic one was present. P terminal force in lead V1 (PtfV1), mentioned the first time by Morris, Estes, Whalen, Thompson, and McIntosh (1964) and defined as terminal duration multiplied by terminal amplitude, was correlated with congestive heart failure and predictive of development of long-term MACEs in ACS (Li et al., 2015; Shah et al., 2016). Prolongation of QRS duration at the time of NSTEMI is often accompanied with a worse left ventricular function and predicts adverse long-term outcome, especially in the setting of left bundle branch block (Baslaib et al., 2010; Jimenez-Candil et al., 2008; Shah et al., 2016).

Therefore, we conducted this study to investigate the long-term prognostic performance of variations of selected ECG parameters during hospitalization, including P-wave duration, PtfV1, QRS duration, and numbers of leads showing ST depression.

2 | MATERIALS AND METHODS

This is a retrospective and single-center study. We recruited patients diagnosed as NSTEMI at discharge between January 2013 and December 2014 in West China Hospital of Sichuan University consecutively. The diagnostic criteria of NSTEMI we acted in accordance with were as follows: A rise of cardiac biomarker values above the 99th percentile upper reference limit (URL) was detected, and at least one of the followings was met: (a) symptoms of myocardial ischemia; (b) associated ECG abnormalities (including new ST depression ≥ 0.05 mV in two contiguous leads and/or T inversion ≥ 0.1 mV in leads with prominent R wave or R/S ratio > 1) without persisting two contiguous leads with ST elevation; (c) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (Thygesen et al., 2012). The subjects enrolled in this study had to meet the following inclusion criteria as well: (a) older than 18 years old; (b) survive the hospitalization and be discharged from hospital upon recovery; (c) the ECGs on admission and discharge were available; (d) equal or greater than 50% stenosis of at least one of the main vessels of coronary arteries was confirmed by coronary angiogram.

Patients with any conditions listed as below were excluded: severe hepatorenal dysfunction, pregnancy, malignant tumors, active bleeding, hematological system diseases, or hypokalemia (blood potassium < 3.5 mM) at admission. Patients with ECG of nonsinus rhythm, branch bundle block were rejected because parts of ECG parameters were unobtainable or deviant. Excluded either were

patients with symptoms completely relieved when arrived at our medical center, who were transferred for elective PCI.

All subjects enrolled were treated in accordance with latest guidelines of NSTEMI management at the time, and the therapeutic process was not interfered with by this study. This study was permitted by the local ethical recommendations of the hospital's committee on human research, and the informed consents were signed by subjects themselves or their legally authorized persons before this study initiated.

2.1 | Clinical data collection and ECG parameter measurement

Standard 12-lead ECGs (25 mm/s and 1 mV, mostly using GE Medical Systems, Milwaukee, WI, USA) were performed on each subject on admission and discharge, respectively. ECGs at admission were defined as recorded at the first medical contact or in our emergency department before revascularization after symptoms arose. ECGs at discharge were defined as the last ECG recorded before patients left hospital at the same stay. Measurements of ECGs were performed manually by using ECG calipers and hand magnifiers. The duration and amplitude of negative P terminal force were measured following the protocol proposed by Morris et al. (1964) when it was present in leads V1. In addition, numbers of leads showing ST depression ≥ 0.1 mV were counted up.

To ensure the reproducibility of the measuring, two medical staffs completed all measurements independently. For every measurement, repeated measuring on three sequential waves in the optimal leads was required, and the median values were recorded as measuring results. Approximate reads of within ± 0.005 s in duration and ± 0.125 mm in amplitude were acceptable. When differences of measuring results between two measurers existed, the average was calculated. The intra-class correlation coefficients (ICC) of intra-measurer variability was 0.758 (0.323–0.929, 95% confidential interval (CI)) for P-wave duration, 0.876 (0.608–0.965, 95% CI) for PtfV1, 0.909 (0.672–0.975, 95% CI) for QRS duration, respectively; the ICC of inter-measurer variability was 0.856 (0.571–0.959, 95% CI), 0.961 (0.867–0.989, 95% CI), 0.755 (0.341–0.927, 95% CI), respectively.

We reviewed each participant's coronary angiogram and divided them into two sorts, single- or multi-vessel lesion. Single-vessel lesion was defined as only one main coronary vessel developing $\geq 50\%$ stenosis, while multi-vessel lesion meant that two or three main vessels were $\geq 50\%$ obstructed. Other associated clinical information was collected for each patient, including smoking history, diabetes mellitus, laboratory test results, heart function grade of NYHA, and GRACE risk score at admission.

Variations of each electrocardiographic measurement of same patients during hospitalization were calculated as Delta: Delta of P-wave duration (Delta-P, ms) was duration of P wave at discharge minus that at admission; Delta of QRS complex duration (Delta-Q, ms) was duration of QRS at discharge minus that at admission; Delta of numbers of leads showing ST depression (Delta-N) was numbers of leads showing ST depression at discharge minus that at admission. Positive delta values and zero were designated as Delta (+) while negative were Delta (-). We assigned subjects into two groups, respectively, according to these three

categories above, Delta (+) group and (-) group. Patients with Delta-P (-) were assigned to "reduction" group while Delta-P (+) were assigned to "no reduction" group; Patients with Delta-Q (-) were assigned to "not prolonged" group while Delta-Q (+) to "prolonged" group; Patients with Delta-N (-) were assigned to "no depression or decrease" group while Delta-N (+) to "no change or increase" group. As for PtfV1, ≤ -0.03 (mm * s) was considered as PtfV1 positive, while > -0.03 (mm * s) was negative. According to different changing trend of PtfV1 values during hospitalization, we assigned subjects into four groups: If the values of PtfV1 during hospitalization were consistent, patients were assigned into persistent (PtfV1) negative or positive group; if the values were inconsistent, then into other two groups: normalization group for patients showing positive PtfV1 at admission but turning to negative at discharge, new-onset positive group for patients with the opposite trend.

2.2 | Follow-up and statistics analysis

Follow-up was done by coworkers, who did not take part in prior clinical information collection and analysis, mainly through conducting telephone follow-up to patients themselves or their close family

members. Whether and when events occurred and whether patients were taking medication as prescribed were collected. The average of follow-up time was 38.4 (± 16.1) months, and the rate of loss to follow up was 7.6%. All follow-up results were consistent with electronic medical records system in our center.

The primary endpoint in this study was a composite endpoint of major adverse cardiovascular events (MACEs), including nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. The second endpoint was a composite endpoint of all-cause death, nonfatal stroke, nonfatal myocardial infarction, and readmission due to heart failure.

Continuous variables were presented as mean $\pm$ SD or median (interquartile range) and categorical variables as percentage or frequency. Comparisons of baseline data between groups were performed using one-sample *t* test for continuous variables or Pearson χ^2 test for categorical variables. The Kaplan-Meier estimate was conducted for survival analysis, and differences between groups were assessed using a log-rank test. Factors with $p \leq 0.10$ analyzed by univariate analysis were taken into Cox proportional hazards model. Two-sided p value < 0.05 was considered statistically significant. All

TABLE 1 Clinical baseline data of all patients and groups divided by P-wave duration

	All patients (N = 170)	P-wave duration		p-Value
		Reduction (N = 62)	No reduction (N = 108)	
Gender, male	140 (82.4%)	53 (85.5%)	87 (80.6%)	0.417
Age (years)	65.7 $\pm$ 11.2	66.4 $\pm$ 11.2	65.3 $\pm$ 11.3	0.533
PCI or CABG	10 (5.9%)	5 (8.1%)	5 (4.6%)	0.360
Stroke	12 (7.1%)	5 (8.1%)	7 (6.5%)	0.698
Diabetes mellitus	44 (25.9%)	17 (27.4)	27 (25.0%)	0.729
History of smoke	109 (64.1%)	41 (66.1%)	68 (63.0%)	0.679
COPD	19 (11.2%)	7 (11.3%)	12 (11.1%)	0.972
HTN (stage 1/2/3)	16/27/62	9/11/20	7/16/24	0.261
SBP (mmHg)	124 $\pm$ 23.5	123 $\pm$ 21	125 $\pm$ 25	0.480
Heart rate (b/min)	77.2 $\pm$ 13.1	76 $\pm$ 13	78 $\pm$ 13	0.406
Creatinine (μ M)	94.9 $\pm$ 34.7	91.0 $\pm$ 34.3	97.2 $\pm$ 35.0	0.480
Uric acid (μ M)	363.9 $\pm$ 106.2	364.8 $\pm$ 111.3	363.4 $\pm$ 103.6	0.935
TG (mM)	1.73 $\pm$ 1.23	1.75 $\pm$ 0.96	1.71 $\pm$ 1.36	0.207
TC (mM)	4.35 $\pm$ 1.15	4.27 $\pm$ 1.11	4.39 $\pm$ 1.17	0.551
HDL-C (mM)	1.20 $\pm$ 0.40	1.13 $\pm$ 0.23	1.24 $\pm$ 0.47	0.084
LDL-C (mM)	2.62 $\pm$ 0.95	2.65 $\pm$ 0.95	2.59 $\pm$ 0.96	0.720
Pro-BNP (pg/ml)	2,086 $\pm$ 3,564	1,489 $\pm$ 1,933	2,424 $\pm$ 4,187	0.102
TPN-T (ng/L)	1,430.2 $\pm$ 1,850.3	1,287.7 $\pm$ 1,700.0	1,512.0 $\pm$ 1,934.2	0.448
Multiple-vessel lesion	118 (69.4%)	44 (71.0%)	74 (68.5%)	0.739
No. of stents implant	1.36 $\pm$ 1.1	1.3 $\pm$ 1.0	1.4 $\pm$ 1.2	0.701
Killip class (I/II/III/IV)	69/72/24/5	25/28/8/1	44/44/16/4	0.832
Ad. GRACE score	156 $\pm$ 38	158 $\pm$ 39	155 $\pm$ 37	0.652
Follow-up time	38.4 $\pm$ 16.1	41.1 $\pm$ 14.0	37.0 $\pm$ 17.0	0.130

Note. Ad. GRACE score: admission GRACE score; HDL-C: high-density lipoprotein cholesterol; HTN: hypertension; LDL-C: low-density lipoprotein cholesterol; No. of stents implant.: number of stents implanted; Pro-BNP: pro-brain natriuretic peptide; SBP: systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; TPN-T: troponin T.

data analyses were performed using windows software IBM SPSS statistics, version 22.

3 | RESULTS

A total of 170 patients with 140 males were included in our study. Clinical characteristics of all subjects and groups divided by P-wave duration were shown in Table 1. The maximum age in our study was 90 years, the minimum was 39, and the mean of age was 65.7 ± 11.2 . There were totally 10 subjects (5.9%) undergoing percutaneous coronary intervention (PCI) or Coronary artery bypass grafting before recruitment; 12 (7.1%) with a history of stroke; 109 (64.1%) in a habit of smoking. 44 patients (25.9%) were diagnosed with type II diabetes mellitus, 19 (11.2%) as chronic obstructive pulmonary disease, 105 (61.8%) as hypertension. The Killip class and Grace score were also listed in Table 1. Comparison of patients' baseline.

Data and medical history between groups were not found statistically significant. Vital signs such as systolic pressure and heart rate recorded at admission, laboratory test results of blood fat, urine creatinine, BNP, and TPN-T were analyzed and listed separately, and no statistical significance was found either comparing between groups.

In this study, total 340 ECGs of 170 patients were taken into scrutiny.

3.1 | P-wave duration

P-wave duration in this study differed from 50 to 140 ms. The average of P-wave duration was not significant between admission

and discharge [99 ± 15 ms vs. 97 ± 14 ms, $p = 0.071$]. There were 33.5% of admission ECGs and 27.1% of discharge ECGs showing P wave ≥ 110 ms duration. By comparing the P-wave duration at discharge and admission, differences between at discharge and admission, namely Delta-P, ranged from -40 to 30 ms. Discharge P wave showing IAB between groups was 17.5% versus 32.7%, $p = 0.033$. The primary endpoint events of each group were 5 (8.1%) versus 21 (19.4%), $p = 0.047$. The survival time estimated using Kaplan–Meier method was 56.8 (54.1–59.5, 95% CI) versus 50.3 (46.5–54.0, 95% CI) months, which was found statistically significant ($p = 0.041$). The secondary endpoint events were 9 (14.5%) versus 28 (25.9%), and further survival analysis using K–M method showed no statistical significance ($p = 0.084$).

3.2 | P-wave terminal force in lead V1

In present study, PtfV1 values ranged from 0 to -0.9000 mm * s, and positive rate was 49.4% for admission, 47.6% for discharge, respectively. By comparing PtfV1 between admission and discharge, subjects were assigned into four groups according to different PtfV1 changing trend. The primary endpoint events of each group were 8 (8.1%), 3 (11.5%), 7 (31.2%), 8 (13.3%), and the estimated survival time were 54.3 (50.5–58.1, 95%CI), 54.7 (48.8–60.3, 95% CI), 41.7 (33.0–50.5, 95% CI), 52.6 (50.0–55.2, 95% CI) months, respectively. Comparison between groups using Log-rank test showed statistically significant ($p = 0.039$). The further comparison between any two groups showed that “new-onset positive” group had shortest estimated survival period ($p = 0.013$; $p = 0.049$; $p = 0.034$, respectively).

TABLE 2 Primary endpoint events and survival analysis of groups categorized by four selected electrographic parameters

Electrographic parameters	Primary endpoint events	<i>p</i> Value ^a	Estimated survival time (months)	95% confidence interval	<i>p</i> Value ^b
P-wave duration					
Reduction (<i>n</i> = 62)	5 (8.1%)	0.047	56.8	54.1–59.5	0.041
No reduction (<i>n</i> = 108)	21 (19.4%)		50.3	46.5–54.0	
PtfV1					
Per. negative (<i>n</i> = 62)	8 (8.1%)	0.147	54.3	50.5–58.1	0.039
Normalization (<i>n</i> = 26)	3 (11.5%)		54.7	48.8–60.3	
New. positive (<i>n</i> = 22)	7 (31.2%)		41.7	33.0–50.5	
Per. positive (<i>n</i> = 60)	8 (13.3%)		52.6	50.0–55.2	
QRS duration					
Not prolonged (<i>n</i> = 125)	16 (12.8%)	0.132	54.0	51.2–56.7	0.120 ^c
Prolonged (<i>n</i> = 45)	10 (22.2%)		48.8	42.7–55.0	
ST-segment depression					
No depression or decrease (<i>n</i> = 97)	10 (10.3%)	0.037	55.7	53.2–58.2	0.025
No change or increase (<i>n</i> = 73)	16 (21.9%)		48.6	43.7–53.6	

Note. new. positive: new-onset positive; per. negative/positive: persistent negative/positive; PtfV1: P-wave terminal force in V1.

^aComparison of event rate using Pearson χ^2 test. ^bComparison of survival status using Kaplan–Meier survival estimate. ^cComparison with Breslow test showed statistically significant difference ($p = 0.049$).

3.3 | QRS duration

The mean value of QRS duration was 90.41 ± 12.65 ms versus 90.76 ± 10.88 ms (admission vs. discharge, $p = 0.691$). Patients with prolonged QRS at discharge compared to that at admission seemed to have higher rate of primary endpoint events (22.2% vs. 12.8%, $p = 0.132$). The estimated survival period was 54.0 (51.2–56.7, 95% CI) versus 48.8 (42.7–55.0, 95% CI) months, respectively. Comparison of between-group survival status using K-M method showed no statistical significance ($p = 0.120$).

3.4 | Number of leads showing ST-segment depression

The rate of MACEs during follow-up was 10.3% versus 21.9%, $p = 0.037$. The estimated survival time was 55.7 (53.2–58.2, 95% CI) versus 48.6 (43.7–53.6, 95% CI) months, and the result was statistically significant ($p = 0.025$).

All results above were shown in Table 2. Survival diagrams were drawn respectively in Figure 1.

All possible cofounders and ECG parameters were taken into a Cox proportional hazards model analysis. The outcome showed that diabetes mellitus, hypertension stage 3, multiple-vessel lesion, new-onset PtfV1 positive group, QRS duration-prolonged group were independent risk factors for the primary endpoints in NSTEMI patients. The Hazards ratio and p-value were presented separately in Table 3.

4 | DISCUSSION

This study reviewed 170 NSTEMI patients' ECGs recorded at admission and discharge and assessed the prognostic value of dynamic changes in ECG parameters including P-wave duration, PtfV1, QRS duration, and numbers of leads showing ST-segment depression. According to the results, patients with no reduction of P-wave duration, new-onset PtfV1 positive, no change or increase in number of leads with ST-segment depression seem to have a higher risk to MACEs and a relatively worse prognosis.

As we know it, P wave is generated by the depolarization of atrium and a sign of atrial excitement, while QRS complex is a reflection of

FIGURE 1 Survival curves based on four ECG parameters. Abbreviation as in Table 2

TABLE 3 Multivariate cox proportional regression analysis of predictors for MACEs

Factors ^a	p-Value	HR	95%CI
Diabetes mellitus	0.042	2.673	1.038–6.884
Stage 3 hypertension	0.010	5.532	1.515–20.202
Multiple-vessel lesion	0.001	5.344	2.060–13.863
New-onset PtfV1 positive	0.011	5.150	1.450–18.291
Prolonged QRS duration	0.034	1.954	1.050–3.634

^aOther factors taken into analysis were as follows: gender, age, P-wave duration, number of leads showing ST-segment depression, Killip classification, GRACE score at admission.

depolarization of ventricle. Prolongation of conduction ($p > 110$ ms; QRS >100 ms) could be associated with chamber dilatation or muscular hypertrophy, intra-atrial/ventricular conduction delay, elevated chamber pressure, impaired ventricular distensibility (Hancock et al., 2009). Especially when P-wave duration is ≥ 110 ms, which indicates IAB and is a risk factor for congestive heart failure (Goyal & Spodick, 2001). Conformed by timely coronary angiogram, NSTEMI patients enrolled in present study lacked in blood flow in at least one of coronary arteries in different levels, causing acute myocardial ischemia and possibly leading to heart failure. The abnormalities of ventricular wall motion because of myocardial ischemia would result in elevation of left ventricular filling pressure and hemodynamic disorders, leading to anatomic atrial/ventricular dilatation or chamber pressure overload and excitement conduction changed with it. Comparing P-wave duration at admission and discharge, the recovering of P-wave duration correlates with improvement of heart function and indicates a better prognosis (Proietti et al., 2012). In present study, the outcomes differed in patients with different changing trend of P-wave duration and the reduction of P-wave reduction group had a lower rate for MACEs and better survival in comparison with no reduction of P-wave duration group. However, the same effect of QRS prolongation was not observed, and the mechanism was unclear. The ischemic damage directly to the heart conduction system might interfere with QRS morphology and duration and result would be uncertain. Therefore, careful observation of changes of P-wave duration was clinically useful and could provide information to predict the chance of MACEs in NSTEMI patients.

As addressed in prior studies, dynamic changes in P-wave terminal force in lead V1 (PtfV1) were found to correlate with acute changes in the state of cardiac function and were specific for left atrial enlargement (Birkbeck, Wilson, Hall, & Meyers, 2006; Heikkila, Hugenholtz, & Tabakin, 1973). The present study showed that patients developing new-onset PtfV1 exceeding $0.03 \text{ mm} \cdot \text{s}$ in negative value during hospitalization had a higher rate for MACEs after discharge and worse survival time during follow-up. However, patients with persisting positive PtfV1 showed no difference in event incidence or survival time, which was partially inconformity with a preceding study (Li et al., 2015). A portion of patients with

PtfV1 positive at admission might be caused by chronic left atrial enlargement or old myocardial scars and was not due to impairment of acute myocardial infarction. Moreover, the study population was not completely consistent between two studies.

ST-segment depression is proved to associate with myocardial ischemia and patients presented with ST-segment depression in any leads indicate a worse prognosis than those with normal ST segment. However, the quantitative analysis of leads with ST-segment depression seems no additional help to predict outcomes in follow-up (Holmvang et al., 2003; Kaul et al., 2001; Yan et al., 2006). In results of current study, differences of survival were found between patients grouped by changes in number of leads with ST depression from admission to discharge. After revascularization and standard medicine therapies, comparing it between discharge and admission, no change or even increase in number of leads showing ST-segment depression might suggest a higher risk of adverse events and worse survival outcomes during follow-up.

5 | LIMITATIONS

This study was a retrospective observational study and conducted with a relatively small sample size, which would cause biases and reach an underpowered conclusion. In this study, although we tried to minimize the measuring error, it might still interfere the power of argument and the final conclusions. Besides, the population of this study was a specific portion of MI patients, so the extension of conclusions was limited relatively.

6 | CONCLUSION

A 12-leads ECG is commonly seen as an essential and inexpensive modality for diagnosis and risk stratification for ACS patients. This study made an attempt to uncover relationship of ECG parameters changes and long-term prognosis. According to this study, it suggests that discharge ECG with new-onset PtfV1 positive and prolonged QRS duration comparing to admission were independent predictors for MACEs in NSTEMI patients. The differences of ECG parameters between at admission and discharge, including P-wave duration, number of leads with ST-segment depression, carried long-term prognostic information for NSTEMI patients.

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