Effects of nicorandil infusion on ECG parameters in patients with unstable angina pectoris and percutaneous coronary intervention

Weiding Wang MD, PhD† | Xu Zhang BS† | Kangyin Chen MD, PhD† | Li Yin MD, PhD† | Mengqi Gong BS† | Yang Liu BS† | Gary Tse MD, PhD† | Lin Wu MD, PhD‡,³ | Guangping Li MD, PhD† | Tong Liu MD, PhD†

ORIGINAL ARTICLE

Abstract

Background: Percutaneous coronary intervention (PCI) is effective in treating patients with acute coronary syndrome (ACS) but is associated with some serious complications. Nicorandil is an anti-anginal agent acting to improve microvascular circulation and to increase coronary blood flow. The objective of this article is to evaluate the effects of intracoronary injection followed with continuous intravenous injection of nicorandil on ECG parameters in patients with unstable angina pectoris (UA) undergoing PCI.

Methods: A single-center, self-controlled clinical trial was conducted at the Second Hospital of Tianjin Medical University between January 2019 and April 2019. Sixty-three consecutive patients with UA who received coronary angiography and selective PCI were enrolled. ECG was recorded and analyzed before and 24 hr after nicorandil infusion.

Results: Patients were divided into three groups: control group (n = 23, aged 63.43 ± 12.55 years), short-term, and prolonged use with nicorandil group (n = 20 and 20, aged 66.45 ± 8.06 years and 65.80 ± 9.49 years, respectively). Clinical characteristics and ECG parameters were similar before PCI among three groups (p > .05). In nicorandil treatment groups, intervals of QTd and Tp-e in patients post-PCI were significantly shorter than that in control and pre-PCI (p < .05).

Conclusions: Nicorandil infusion reduces QTd and Tp-e interval in patients with UA. Further studies will be needed to determine whether these electrophysiological changes are associated with a reduction of ventricular arrhythmias and improved outcomes.

KEYWORDS

nicorandil, QT dispersion, Tp-e interval, unstable angina pectoris
Coronary heart disease (CHD) is caused by stenosis or obstruction of the coronary vascular lumen due to atherosclerosis, leading to myocardial ischemia, angina pectoris, and/or infarction (Li, Pan, Dai, Liu, & Zhang, 2016). Due to the advance in treatment options and drug development, CHD has become a long-term chronic disease which remains a major public health burden (Sajobi et al., 2018). Over the past years, although the overall mortality from CHD is steadily decreasing, the prevalence of CHD is still rising rapidly, especially in developing countries (Ebrahim & Smith, 2001).

Nicorandil, a mitochondrial ATP-dependent potassium (K-ATP) channel opener and a nitric oxide donor, is an agent commonly used to improve ischemic symptoms in CHD patients with multiple pharmacological mechanisms of action (Kostic et al., 2015). It opens the K⁺-ATP channels in the vascular smooth muscle cells, thus increasing K⁺ efflux and in turn inhibiting Ca²⁺ influx. Consequently, cells are relieved from calcium overload, and this process is also associated with a decreased incidence of arrhythmias. Thus, it can relax small coronary arteries and increase the blood flow into the myocardium. Finally, the nitrate-like action of nicorandil acting as a vasodilator improves the symptoms of angina pectoris (Markham, Plosker, & Goa, 2000; Taira, 1989).

Intracoronary injection of nicorandil can be used to prevent severe no-reflow phenomenon during percutaneous coronary intervention (PCI). It also reduces the occurrence of the slow-flow phenomenon by improving microvascular circulation in patients with acute myocardial infarction (AMI) (Lee et al., 2008). However, to the best of our knowledge, a few studies have investigated whether intracoronary injection combined with continuous intravenous injection of nicorandil on ECG parameters in patients with unstable angina pectoris (UA) underwent PCI.

2 | MATERIAL AND METHODS

2.1 | Study design

A single-center, self-controlled clinical trial was conducted at the Second Hospital of Tianjin Medical University, Tianjin, China, between January 2019 and April 2019. A total of 63 consecutive patients with UA who received coronary angiography and selective PCI were enrolled. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki and approved by the Medical Ethics Committees of the Second Hospital of Tianjin Medical University. Written informed consent was obtained from all study participants.

2.2 | Patients enrolled and selection criteria

The inclusion criteria were as following: (a) all patients were diagnosed with UA and received coronary angiography and selective PCI; (b) all patients were informed and agreed to participate in this study; the exclusion criteria included the following: (a) history of myocardial infarction and diagnosed with acute myocardial infarction; (b) complete left or right bundle branch block; (c) atrial flutter or fibrillation; (d) acute heart failure; (e) history of ventricular pacemaker implantation; (f) severe liver and renal insufficiency or electrolyte abnormalities; (g) complications during angioplasty (acute stent thrombosis, coronary dissection, and adjacent vessels lost, etc); (h) patients who were presently receiving nicorandil; (i) patients who had history of coronary artery bypass grafting (CABG).

The study subjects were divided into three groups: group A (control, treated with intracoronary injection of 10 ml of saline, and then continuous intravenous injection with saline within 6 hr after PCI, n = 23), group B (short-term use of nicorandil treatment group, treated with intracoronary injection of 0.5 mg in 10 ml saline of nicorandil, and then continuous intravenously injected with 12 mg of nicorandil at a rate of 2 mg/hr within 6 hr after PCI, n = 20), and group C (prolonged infusion of nicorandil treatment group, intracoronary injection of 0.5 mg in 10 ml of nicorandil, and then continuous intravenous injection with 48 mg of nicorandil at a rate of 2 mg/h within 24 hr after PCI, n = 20). All subjects were blinded to the study groups.

All patients underwent routine blood tests and echocardiography. Diagnostic coronary angiography was performed, and drug-eluting stent (DES) implantation was furrowed via the radial artery access. Oral administrations of drugs were used according to the current standard guidelines and clinical practice for the management of patients with UA. Patients with comorbidity of other diseases including hypertension and diabetes mellitus (DM) were treated with corresponding drugs.

Patient information collected including age, sex, diabetes, hypertension, smoking and drinking history, serum creatinine, uric acid, blood urea nitrogen (BUN), serum sodium and potassium, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose, hemoglobin, cardiac troponin I (cTnI), creatine kinase (CK), creatine kinase isoenzyme MB (CK-MB), and echocardiographic parameters.

2.3 | ECG measurements

Standard 12-lead electrocardiograms at a paper speed of 50 mm/s and a gain of 10 mm/mV were recorded at 24 hr before nicorandil use and 24 hr after nicorandil use. ECG parameters were measured including the following: heart rate (HR), P-wave duration, P-wave amplitude, P-wave dispersion, PR interval, QRS duration, T-wave amplitude, QT interval, corrected QT interval (QTc), QT dispersion (QTD), and peak-to-end interval of the T wave (Tp-e).

The PR interval was measured from the beginning of the P wave to the beginning of the QRS complex on the basis of millisecond (ms). The P-wave dispersion was measured from the difference between the maximum and minimum P-wave duration in the 12-lead ECG.
The QT interval was measured from the beginning of the QRS complex to the end of the T wave in ms (usually V1-V3). The QTc was calculated using the equation of Bazett’s formula. The QT dispersion (QTd) was measured from the difference between the maximal and minimal QT intervals in the 12-lead ECG in ms. The T-wave amplitude was measured in the precordial lead where it was most prominent on the baseline ECG (usually V1-V3). None of the patients had an U wave fused with the terminal portion of the T wave. The Tp-e was measured from the peak of T wave to the end of T wave in ms. ECG measurements were performed by 2 independent cardiologists, and the average values were used for data analysis.

2.4 | Main outcomes

The main outcome of this study was to evaluate the effect of intracoronary injection followed with intravenous injection of nicorandil on ECG changes in patients with UA during selective PCI.

2.5 | Statistical analysis

Data were analyzed statistically using IBM SPSS version 19 software. All values are expressed as means ± standard deviation (SD), and categorical variables are described as a number (percentage). Continuous variables were compared using analysis of variance (ANOVA), and proportions were compared using the chi-square or Fisher’s exact tests. Categorical variables were compared using the chi-squared test. Comparisons in the same group between before and after treatment were conducted using matching t test. A value of p < .05 was considered as a statistically significant difference.

3 | RESULTS

A total of 63 consecutive patients with UA who received coronary angiography and selective PCI were enrolled into the study. The patients were divided into three groups: group A (control group, n = 23, mean age 63.43 ± 12.55 years, male 14), group B (n = 20, mean age 66.45 ± 8.63 years, male 12), and group C (n = 20, mean age 65.80 ± 9.49 years, male 15). The clinical characteristics of the patients in the control and nicorandil treatment groups are summarized in Table 1. There were no differences between the three groups in terms of age, sex, smoking and drinking history, comorbidity, results of laboratory blood test, and echocardiographic parameters (Table 1).

There were no significant statistical differences in ECG parameters at baseline before PCI among the three groups (Table 2). After saline infusion in control group, no statistically significant differences were identified in ECG parameters (Tables 3 and 4). However, both QTd and Tp-e were significantly shortened in the short-term use and prolonged infusion of nicorandil groups. QTd values were also decreased from 43.95 ± 11.16 ms and 39.16 ± 13.74 ms to 30.85 ± 8.63 ms and 29.05 ± 10.19 ms (p < 0.05), respectively, in two nicorandil infusion groups (Figure 1). Tp-e intervals were shortened from 99.50 ± 15.71 ms and 99.12 ± 18.61 ms to 80.50 ± 20.38 ms and 86.11 ± 7.77 ms in the short-term use and prolonged infusion of nicorandil groups, respectively (p < .05, Figure 2).

Furthermore, we combined the two groups (group B and group C) to increase statistical power changes in QTc duration. However, there was no statistically significant difference in QTc interval before and after nicorandil infusion in combined B and C groups. QTd was decreased from 41.10 ± 15.51 ms to 29.82 ± 9.15 ms (p < .05), and Tp-e intervals were also shortened from 98.87 ± 13.70 ms to 83.50 ± 15.61 ms (p < .05) following nicorandil infusion in combined B and C groups (Table 5).

4 | DISCUSSION

The main finding of this study includes that nicorandil at short-term use and prolonged infusion significantly reduced the repolarization dispersion, that is, QT dispersion and Tp-e intervals, which may potentially, at least in part, reflect the cardioprotective effects of nicorandil(Qi et al., 2018; Takabatake et al., 2015). Wu, et al reported that intracoronary injection of nicorandil did not achieve the expected clinical benefit (Wu, Huang, Xie, & Zhou, 2013), may be due to the short half-life of the drug (approximately 1 hr). In this study, continuous intravenous injection of nicorandil was performed after intracoronary short-term use of the drug.

4.1 | Mechanism of action and clinical effects of nicorandil

Nicorandil is an anti-anginal agent that increases coronary blood flow and improves microvascular circulation. It activates the mitochondrial ATP-sensitive potassium (KATP) channels in the vascular smooth muscle cells, thus increasing the outflow of K+ from cells and then inhibiting Ca2+ influx. As a result, it causes membrane hyperpolarization, shortens action potential duration and reduces Ca2+ overload and arrhythmic burden. Moreover, it has nitrate action leads to vascular smooth muscle relaxation and a reduction of coronary vascular resistance, cardiac preload and afterload (Markham et al., 2000; Taira, 1989). Recently, Lei et al. proposed that nicorandil was subclassified as a class IIIb anti-arrhythmic agent because of its potential effects on the I_KATP channels (Lei, Wu, Terrar, & Huang, 2018).

Clinical studies have confirmed the cardiac protective effects of nicorandil. IONA was a randomized placebo-controlled trial of 5,126 patients with stable angina with a mean follow-up of 1.6 years. Compared to the placebo, nicorandil treatment was associated with lower rates of major cardiovascular events, including nonfatal acute myocardial infarction and sudden cardiac death, in patients with stable angina (“Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial,” IONA Study Group, 2002). CESAR 2 trial is another
| Parameters                      | Group A (n = 23) | Group B (n = 20) | Group C (n = 20) | χ²/F value | p value |
|--------------------------------|-----------------|-----------------|-----------------|------------|---------|
| Age (years)                    | 63.43 ± 12.55   | 66.45 ± 8.06    | 65.80 ± 9.49    | 0.514      | NS      |
| Male, n (%)                    | 14 (61%)        | 12 (60%)        | 15 (75%)        | 1.273      | NS      |
| Smokers, n (%)                 | 11 (48%)        | 9 (45%)         | 1 (60%)         | 1.028      | NS      |
| Hypertension, n (%)            | 16 (70%)        | 16 (80%)        | 14 (70%)        | 0.762      | NS      |
| T2DM, n (%)                    | 6 (26%)         | 7 (35%)         | 11 (55%)        | 3.911      | NS      |
| Laboratory findings            |                 |                 |                 |            |         |
| Triglycerides (mmol/L)         | 1.99 ± 2.59     | 1.96 ± 1.19     | 2.11 ± 1.52     | 0.032      | NS      |
| Total cholesterol (mmol/L)     | 4.50 ± 1.08     | 4.39 ± 0.96     | 4.35 ± 1.07     | 0.128      | NS      |
| HDL (mmol/L)                   | 1.14 ± 0.25     | 1.06 ± 0.25     | 1.01 ± 0.23     | 1.580      | NS      |
| LDL (mmol/L)                   | 2.77 ± 0.86     | 2.75 ± 0.83     | 2.75 ± 0.98     | 0.002      | NS      |
| ALT (U/L)                      | 22.58 ± 9.55    | 26.54 ± 22.14   | 17.45 ± 6.80    | 2.041      | NS      |
| AST (U/L)                      | 29.23 ± 46.64   | 21.55 ± 11.84   | 19.58 ± 14.43   | 0.625      | NS      |
| Hemoglobin (g/L)               | 139.47 ± 12.50  | 135.05 ± 17.08  | 139.05 ± 16.63  | 0.518      | NS      |
| Sodium (mmol/L)                | 142.31 ± 2.30   | 141.02 ± 3.08   | 141.94 ± 3.29   | 1.101      | NS      |
| Potassium (mmol/L)             | 4.08 ± 0.33     | 4.01 ± 0.54     | 4.16 ± 0.30     | 0.689      | NS      |
| Creatinine (µmol/L)            | 66.43 ± 16.36   | 68.19 ± 20.45   | 72.99 ± 11.63   | 0.884      | NS      |
| Uric acid (µmol/L)             | 324.09 ± 105.40 | 306.78 ± 70.38  | 331.43 ± 107.89 | 0.345      | NS      |
| BUN (mmol/L)                   | 5.49 ± 1.49     | 5.52 ± 1.43     | 5.16 ± 1.43     | 0.392      | NS      |
| FBG (mmol/L)                   | 6.08 ± 1.12     | 7.34 ± 2.95     | 6.51 ± 1.95     | 1.943      | NS      |
| cTnI (ng/ml)                   | 0.002 ± 0.001   | 0.003 ± 0.002   | 0.002 ± 0.001   | 2.931      | NS      |
| CK (U/L)                       | 99.08 ± 59.25   | 86.30 ± 30.66   | 69.35 ± 25.85   | 2.636      | NS      |
| CK-MB (U/L)                    | 14.96 ± 6.38    | 14.77 ± 10.17   | 1.015 ± 4.31    | 2.845      | NS      |
| Echocardiographic parameters   |                 |                 |                 |            |         |
| LAD (mm)                       | 38.26 ± 5.23    | 29.93 ± 7.27    | 39.98 ± 4.17    | 0.472      | NS      |
| LVEDD (mm)                     | 45.98 ± 12.28   | 50.40 ± 6.33    | 50.06 ± 4.09    | 1.335      | NS      |
| LVESD (mm)                     | 30.65 ± 6.77    | 31.93 ± 9.68    | 30.83 ± 5.52    | 0.128      | NS      |
| IVS (mm)                       | 9.18 ± 1.35     | 10.02 ± 2.52    | 9.18 ± 1.19     | 1.135      | NS      |
| LVEF (%)                       | 62.06 ± 5.93    | 59.35 ± 5.89    | 61.00 ± 4.83    | 0.890      | NS      |
| Coronary angiography           |                 |                 |                 |            |         |
| Number of patients receiving PCI | 21(91%)       | 19(95%)        | 20(100)        | 1.787      | NS      |
| Number of vessels under stenting | 1.14 ± 0.36   | 1.26 ± 0.45    | 1.05 ± 0.22    | 1.758      | NS      |
| Number of stents per patient  | 1.38 ± 0.59     | 1.63 ± 0.49     | 1.25 ± 0.44     | 2.751      | NS      |
| Medications                    |                 |                 |                 |            |         |
| Aspirin, n (%)                 | 23 (100%)       | 20 (100%)       | 20 (100%)       | –          | NS      |
| β-Blocker, n (%)               | 10 (44%)        | 14 (70%)        | 12 (60%)        | 3.170      | NS      |
| ACEI/ARB, n (%)                | 8 (35%)         | 13 (65%)        | 9 (45%)         | 3.997      | NS      |
| CCB, n (%)                     | 8 (35%)         | 11 (55%)        | 6 (30%)         | 2.975      | NS      |
| Statins, n (%)                 | 23(100%)        | 20 (100%)       | 20 (100%)       | –          | NS      |

Note: Data are presented mean ± SD or n (%).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor antagonist; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CCB, calcium channel blocker; CK, creatine kinase; CK-MB, creatine kinase isoenzyme MB; cTnI, cardiac troponin I; FBG, fasting blood glucose; Group A, control group; Group B, short-term use nicorandil group; Group C, prolonged infusion of nicorandil group; HDL, high-density lipoprotein; IVS, interventricular septum; LAD, left atrial dimension; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; NS, no statistical significance; T2DM, type 2 diabetes mellitus.
multicenter placebo-controlled study including 188 patients with unstable angina, and a lower incidence of nonsustained ventricular tachycardia, supraventricular tachycardia, and transient myocardial ischemia was observed during continuous 48-hr Holter ECG monitoring in the nicorandil group compared to the control group (Patel, Purcell, & Fox, 1999). Izumiya, et al reported that long-term use of oral nicorandil prevented inflammation and oxidative stress, and improved endothelial function and cardiac sympathetic nerve activity in patients with stable angina pectoris (Izumiya et al., 2011).

Kim, et al reported that intravenous administration of nicorandil at 12h before PCI had a myocardial protective effect during PCI in patients with UA (Kim et al., 2005). Oral administration of nicorandil within two hours before PCI reduced the incidences of cardiac damages during PCI and PCI-related myocardial infarction in patients with ACS (Yang et al., 2015). Intravenous administration of nicorandil also improved coronary microcirculation in patients with AMI (Suematsu et al., 2013).

Intracoronary injection of nicorandil during PCI was also beneficial. By reducing the microvascular resistance and increasing coronary flow reserve, intracoronary administration of nicorandil significantly improved microvascular function (Kostic et al., 2015), prevented no-reflow phenomenon, ameliorated myocardial perfusion and cardiac function (Qi et al., 2018), reduced the incidence of reperfusion injury, and improved short-term clinical outcomes during PCI in patients with STEMI (Feng, Liu, Wang, Niu, & Han, 2019). In addition, in a meta-analysis study, nicorandil was shown to be more effective in the Chinese population (Ye, Su, & Li, 2017). Nicorandil was also shown to be safe and well tolerated when it was used in the recommended dosage in a large cohort study (Dunn, Freemantle, Pearce, Wilton, & Mann, 1999).

### TABLE 2
Comparison of baseline ECG parameters in three groups of patients

| Parameters                  | Group A (n = 23) | Group B (n = 20) | Group C (n = 20) | F value | p value |
|-----------------------------|------------------|------------------|------------------|---------|---------|
| Heart Rate (beats/min)      | 68.34 ± 10.02    | 74.70 ± 13.32    | 70.45 ± 10.14    | 1.757   | NS      |
| P-wave duration (ms)        | 101.95 ± 12.58   | 103.50 ± 15.13   | 106.90 ± 13.12   | 0.727   | NS      |
| P-wave amplitude (mV)       | 0.12 ± 0.04      | 0.17 ± 0.08      | 0.14 ± 0.05      | 2.814   | NS      |
| P-wave dispersion (ms)      | 35.86 ± 14.89    | 30.75 ± 11.72    | 38.15 ± 12.77    | 1.634   | NS      |
| PR interval (ms)            | 169.86 ± 30.59   | 167.25 ± 24.85   | 170.35 ± 28.51   | 0.071   | NS      |
| QRS duration (ms)           | 105.26 ± 15.44   | 106.60 ± 18.97   | 100.30 ± 9.59    | 0.965   | NS      |
| T-wave amplitude (mV)       | 0.43 ± 0.26      | 0.49 ± 0.25      | 0.54 ± 0.32      | 0.771   | NS      |
| QT interval (ms)            | 403.86 ± 18.07   | 395.80 ± 27.77   | 394.00 ± 28.07   | 0.984   | NS      |
| QTc (ms)                    | 431.04 ± 19.81   | 435.75 ± 26.29   | 421.95 ± 17.34   | 2.155   | NS      |
| QTd (ms)                    | 36.95 ± 10.91    | 43.95 ± 11.16    | 38.25 ± 13.40    | 2.056   | NS      |
| Tp-e (ms)                   | 99.78 ± 24.19    | 99.50 ± 15.71    | 98.25 ± 11.72    | 0.041   | NS      |

Note: Data are presented mean ± SD.
Abbreviations: Group A, control group; Group B, short-term use nicorandil group; Group C, prolonged infusion of nicorandil group; NS, no statistical significance; QTc, corrected QT interval; QTd, QT dispersion; Tp-e, peak-to-end interval of the T wave.

### TABLE 3
Comparison of ECG parameters following nicorandil use in three groups of patients

| Parameters                  | Group A (n = 23) | Group B (n = 20) | Group C (n = 20) | F value | p value |
|-----------------------------|------------------|------------------|------------------|---------|---------|
| Heart Rate (beats/min)      | 66.34 ± 15.31    | 70.50 ± 8.28     | 66.35 ± 9.06     | 0.879   | NS      |
| P-wave duration (ms)        | 106.13 ± 10.37   | 101.75 ± 15.15   | 106.00 ± 10.46   | 0.868   | NS      |
| P-wave amplitude (mV)       | 0.12 ± 0.02      | 0.15 ± 0.88      | 0.13 ± 0.03      | 0.833   | NS      |
| P-wave dispersion (ms)      | 34.39 ± 12.35    | 25.75 ± 9.77     | 31.60 ± 11.68    | 3.166   | <.05    |
| PR interval (ms)            | 169.82 ± 27.35   | 168.25 ± 21.21   | 163.25 ± 44.79   | 0.234   | NS      |
| QRS duration (ms)           | 104.30 ± 15.74   | 106.65 ± 16.13   | 99.20 ± 8.96     | 1.466   | NS      |
| T-wave amplitude (mV)       | 0.43 ± 0.21      | 0.44 ± 0.22      | 0.42 ± 0.17      | 0.060   | NS      |
| QT interval (ms)            | 415.47 ± 31.02   | 394.60 ± 25.72   | 393.55 ± 20.41   | 4.825   | <.05    |
| QTc (ms)                    | 432.30 ± 28.59   | 430.55 ± 22.80   | 410.40 ± 26.09   | 4.487   | <.05    |
| QTd (ms)                    | 35.69 ± 11.92    | 30.85 ± 8.63     | 28.80 ± 9.74     | 2.578   | NS      |
| Tp-e (ms)                   | 98.17 ± 28.18    | 80.50 ± 20.38    | 86.50 ± 8.12     | 3.761   | <.05    |

Note: Data are presented mean ± SD.
Abbreviations: NS, no statistical significance; Group A, control group; Group B, short-term use nicorandil group; Group C, prolonged infusion of nicorandil group; QTc, corrected QT interval; QTd, QT dispersion; Tp-e, peak-to-end interval of the T wave.
**TABLE 4**  Comparison of ECG parameters before and after nicorandil use

| Parameters                  | Group A (n = 23) | Group B (n = 20) | Group C (n = 20) |
|-----------------------------|-----------------|-----------------|-----------------|
|                             | Before NIC      | After NIC       | p value         | Before NIC      | After NIC       | p value         | Before NIC      | After NIC       | p value         |
| Heart rate (beats/min)      | 68.34 ± 10.02   | 66.34 ± 15.31   | NS              | 74.70 ± 13.32   | 70.50 ± 8.28    | NS              | 70.45 ± 10.14   | 66.35 ± 9.06    | NS              |
| P-wave duration (ms)        | 101.95 ± 12.58  | 106.13 ± 10.37  | NS              | 103.50 ± 15.13  | 101.75 ± 15.15  | NS              | 106.90 ± 13.12  | 106.00 ± 10.46  | NS              |
| P-wave amplitude (mV)       | 0.12 ± 0.04     | 0.12 ± 0.02     | NS              | 0.17 ± 0.08     | 0.15 ± 0.88     | NS              | 0.14 ± 0.05     | 0.13 ± 0.03     | NS              |
| P-wave dispersion (ms)      | 35.86 ± 14.89   | 34.39 ± 12.35   | NS              | 30.75 ± 11.72   | 25.75 ± 9.77    | NS              | 38.15 ± 12.77   | 31.60 ± 11.68   | NS              |
| PR interval (ms)            | 169.86 ± 30.59  | 169.82 ± 27.35  | NS              | 167.25 ± 24.85  | 168.25 ± 21.21  | NS              | 170.35 ± 28.51  | 163.25 ± 44.79  | NS              |
| QRS duration (ms)           | 105.26 ± 15.44  | 104.30 ± 15.74  | NS              | 106.60 ± 18.97  | 106.65 ± 16.13  | NS              | 100.30 ± 9.59   | 99.20 ± 8.96    | NS              |
| T-wave amplitude (mV)       | 0.43 ± 0.26     | 0.43 ± 0.21     | NS              | 0.49 ± 0.25     | 0.44 ± 0.22     | NS              | 0.54 ± 0.32     | 0.42 ± 0.17     | NS              |
| QT interval (ms)            | 403.86 ± 18.07  | 415.47 ± 31.02  | NS              | 395.80 ± 27.77  | 394.60 ± 25.72  | NS              | 394.00 ± 28.07  | 393.55 ± 20.41  | NS              |
| QTc (ms)                    | 431.04 ± 19.81  | 435.75 ± 26.29  | NS              | 435.75 ± 26.29  | 430.55 ± 22.80  | NS              | 421.95 ± 17.34  | 410.40 ± 26.09  | NS              |
| QTd (ms)                    | 36.95 ± 10.91   | 35.69 ± 11.92   | NS              | 43.95 ± 11.16   | 30.85 ± 8.63    | <.05            | 38.25 ± 13.40   | 28.80 ± 9.74    | <.05            |
| Tp-e (ms)                   | 99.78 ± 24.19   | 98.17 ± 28.18   | NS              | 99.50 ± 15.71   | 80.50 ± 20.38   | <.05            | 98.25 ± 11.72   | 86.50 ± 8.12    | <.05            |

Note: Data are presented mean ± SD.
Abbreviations: Group A, control group; Group B, short-term use nicorandil group; Group C, prolonged infusion of nicorandil group; NIC, nicorandil; NS, no statistical significance; QTc, corrected QT interval; QTd, QT dispersion; Tp-e, peak-to-end interval of the T wave.
In this study, two different protocols were selected for the use of nicorandil, short-term use protocol, and prolonged infusion.

4.2 | QTd and TP-E intervals

QT dispersion was used to represent the regional variations in ventricular repolarization and the electrophysiologic excitability of the myocardium. Dispersion of repolarization of the ventricular myocardium is considered to be an important factor in the pathogenesis of arrhythmias (Molnar & Somberg, 2009). QTd reflects the regional heterogeneity in ventricular repolarization (de Bruyne et al., 1998; Lee, Okin, Kligfield, Stein, & Lerman, 1997; Priori, Napolitano, Diehl, & Schwartz, 1994) and may be useful in evaluating the risk of ventricular arrhythmias. An abnormal increase in QTd led to poor prognosis, and a reduction of QTd was associated with a better clinical outcome. In a prospective study including 1839 patients with a mean follow-up period of 3.7 years, an increase in QTd was associated with a significant increase of all-cause and cardiovascular mortality (Okin et al., 2000). There was a correlation between the increase in QTd and the incidence of complex ventricular arrhythmias in patients with mitral valve prolapse (Kulan, Komsuoglu, Tuncer, & Kulan, 1996).

QTd is also a marker of myocardial reperfusion status. Continued intravenous administration of nicorandil for 48h after PCI could reduce QTd and the occurrence of ventricular fibrillation in patients with AMI and successful coronary angioplasty (Ueda et al., 2004). Oral administration of nicorandil prevented the occurrence of ventricular arrhythmias after coronary reperfusion by suppressing the increased QTd in patients with stable angina pectoris (Kato, Kamiyama, Maruyama, Tanaka, & Yoshimoto, 2001). More recently, Suleimani et al showed that the QTd in the nicorandil group was lower than the control group in patients with stable angina after PCI (48.1 ± 14.2 vs. 59.2 ± 15.6 ms) (Suleimani, Eshraghi, Daloei, Hoseini, & Nakhaee, 2017).

The Tp-e interval represents the transmural dispersion index of total dispersion of ventricular repolarization (TDR) and is another important marker in the pathogenesis of arrhythmias (Gupta et al., 2008; Yian & Martin, 2003). Increased Tp-e interval is associated with a greater mortality in patients with Brugada syndrome, long-QT syndrome, and myocardial infarction (MI) (Haarmark et al., 2009; Shimizu et al., 2002; Tse, Gong, Li, et al., 2018; Tse, Gong, Meng, et al., 2018). Increased Tp-e was also found to be strongly
4.3 Study limitations

This study was conducted in a single center and had a relatively small sample size in Chinese subjects. Second, we did not record ECG data at 6 hr following nicorandil infusion. Further studies need to be conducted in multicenters with a larger sample size in other ethnicities to make the results more reliable. A follow-up study focusing on outcomes including arrhythmias and mortality will be needed.

5 CONCLUSIONS

Nicorandil reduces QTd andTp-e interval in patients with UA after PCI. Further studies are needed to determine whether they are associated with improved clinical outcomes.

TABLE 5 Comparison of ECG parameters before and after nicorandil use in two groups of patients

| Parameters                  | Group A (n = 23) | Group B + C (n = 40) |
|-----------------------------|-----------------|----------------------|
|                             | Before NIC      | After NIC            | p value | Before NIC      | After NIC            | p value |
| Heart rate (beats/min)      | 68.34 ± 10.02   | 66.34 ± 15.31        | NS      | 72.57 ± 11.88  | 68.43 ± 8.83         | NS      |
| P-wave duration (ms)        | 101.95 ± 12.58  | 106.13 ± 10.37       | NS      | 105.20 ± 14.08 | 103.84 ± 13.03       | NS      |
| P-wave amplitude (mV)       | 0.12 ± 0.04     | 0.12 ± 0.02          | NS      | 0.15 ± 0.07    | 0.14 ± 0.06          | NS      |
| P-wave dispersion (ms)      | 35.86 ± 14.89   | 34.39 ± 12.35        | NS      | 34.45 ± 12.67  | 28.67 ± 11.03        | <.05    |
| PR interval (ms)            | 169.86 ± 30.59  | 169.82 ± 27.35       | NS      | 168.80 ± 26.44 | 165.75 ± 34.68       | NS      |
| QRS duration (ms)           | 105.26 ± 15.44  | 104.30 ± 15.74       | NS      | 103.45 ± 15.17 | 102.92 ± 13.42       | NS      |
| T-wave amplitude (mV)       | 0.43 ± 0.26     | 0.43 ± 0.21          | NS      | 0.52 ± 0.29    | 0.43 ± 0.19          | NS      |
| QT interval (ms)            | 403.86 ± 18.07  | 415.47 ± 31.02       | NS      | 394.90 ± 27.58 | 394.07 ± 22.92       | NS      |
| QTc (ms)                    | 431.04 ± 19.81  | 432.30 ± 28.59       | NS      | 428.85 ± 23.06 | 420.47 ± 26.25       | NS      |
| QTd (ms)                    | 36.95 ± 10.91   | 35.69 ± 11.92        | NS      | 41.10 ± 15.51  | 29.82 ± 9.15         | <.05    |
| Tp-e (ms)                   | 99.78 ± 24.19   | 98.17 ± 28.18        | NS      | 98.87 ± 13.70  | 83.50 ± 15.61        | <.05    |

Note: Data are presented mean ± SD.

Abbreviations: NS, no statistical significance; Group A, control group; Group B + C, short-term use nicorandil group and prolonged infusion of nicorandil group; QTc, corrected QT interval; QTd, QT dispersion; Tp-e, peak-to-end interval of the T wave; NIC, nicorandil.

ACKNOWLEDGMENTS

This work was supported by grants (81970270, 81570298 to T.L.) from the National Natural Science Foundation of China, and the Research Foundation of Major Science and Technology Projects of Tianjin Municipal Science and Technology Bureau [grant number: 16ZXJJSY00120 to K.C.].

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHORS’ CONTRIBUTION

All authors reviewed and approved the manuscript. Directed this study: Tong Liu. Performed this study: Weiding Wang, Xu Zhang, Kangyin Chen, Li Yin, Mengqi Gong, Yang Liu. Draft the main manuscript: Xu Zhang, Revised the main manuscript: Gary Tse, Lin Wu, Tong Liu. Gave suggestions on this study: Guangping Li.

ETHICS

The study was approved by Second Hospital of Tianjin Medical University the ethics committee (Number, KY2019K072). The study was conducted in accordance with the principles of Declaration of Helsinki.

ORCID

Gary Tse https://orcid.org/0000-0001-5510-1253
Tong Liu https://orcid.org/0000-0003-0482-0738

REFERENCES

de Bruyne, M. C., Hoes, A. W., Kors, J. A., Hofman, A., van Bemmel, J. H., & Grobbee, D. E. (1998). QTc dispersion predicts cardiac mortality in the elderly: The Rotterdam Study. Circulation, 97(5), 467–472. https://doi.org/10.1161/01.CIR.97.5.467
Tse, G., Gong, M., Li, C. K. H., Leung, K. S. K., Georgopoulos, S., Bazoukis, G., … International Health Informatics Study, N. (2018). Tpeak-Tend, Tpeak-Tend/QT ratio and Tpeak-Tend dispersion for risk stratification in Brugada Syndrome: A systematic review and meta-analysis. Journal of Arrhythmia, 34(6), 587–597. https://doi.org/10.1002/joa3.12118

Tse, G., Gong, M., Meng, L., Wong, C. W., Georgopoulos, S., Bazoukis, G., … Liu, T. (2018). Meta-analysis of Tpeak-Tend and Tpeak-Tend/QT ratio for risk stratification in congenital long QT syndrome. Journal of Electrocardiology, 51(3), 396–401. https://doi.org/10.1016/j.jelectrocard.2018.03.001

Ueda, H., Nakayama, Y., Tsumura, K., Yoshimaru, K., Hayashi, T., & Yoshikawa, J. (2004). Intravenous nicorandil can reduce the occurrence of ventricular fibrillation and QT dispersion in patients with successful coronary angioplasty in acute myocardial infarction. Canadian Journal of Cardiology, 20(6), 625–629.

Wu, M., Huang, Z., Xie, H., & Zhou, Z. (2013). Nicorandil in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: A systematic review and meta-analysis. PLoS ONE, 8(10), e78231. https://doi.org/10.1371/journal.pone.0078231

Yan, G. X., & Martin, J. (2003). Electrocardiographic T wave: A symbol of transmural dispersion of repolarization in the ventricles. Journal of Cardiovascular Electrophysiology, 14(6), 639–640. https://doi.org/10.1046/j.1540-8167.2003.03155.x

Yang, J., Zhang, J., Cui, W., Liu, F., Xie, R., Yang, X., … Geng, X. (2015). Cardioprotective effects of single oral dose of nicorandil before selective percutaneous coronary intervention. The Anatolian Journal of Cardiology, 15(2), 125–131. https://doi.org/10.5152/akd.2014.5207

Ye, Z., Su, Q., & Li, L. (2017). The clinical effect of nicorandil on perioperative myocardial protection in patients undergoing elective PCI: A systematic review and meta-analysis. Scientific Reports, 7, 45117. https://doi.org/10.1038/srep45117

How to cite this article: Wang W, Zhang X, Chen K, et al. Effects of nicorandil infusion on ECG parameters in patients with unstable angina pectoris and percutaneous coronary intervention. Ann Noninvasive Electrocardiol. 2020;25:e12736. https://doi.org/10.1111/anec.12736