Red Blood Cell Distribution Width is Independently Correlated With Diurnal QTc Variation in Patients With Coronary Heart Disease

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Abstract: To investigate the relationship between red blood cell distribution width (RDW) and diurnal corrected QT (QTc) variation in patients with coronary heart disease.

This retrospective study included 203 patients who underwent coronary angiography between February 2013 and June 2014. RDW values and dynamic electrocardiography (Holter) results were collected to investigate the relationship between RDW and diurnal QTc variation.

Patients were separated into three groups (A, B, and C) by binning their RDW values in an ascending order. RDW values, coronary artery scores and diurnal QTc variations were significantly different among these groups ($P < 0.05$). While coronary artery scores gradually rose with increased RDW, diurnal QTc variation decreased. Pearson’s correlation analysis was applied to control for confounding factors, and multiple correlation analysis showed that coronary artery score was positively correlated with RDW ($r = 0.130$, $P = 0.020$), while it was not correlated with the diurnal QTc variation ($r = -0.226$, $P = 0.681$). RDW was negatively correlated with diurnal QTc variation ($r = -0.197$, $P = 0.035$).

RDW is independently associated with diurnal QTc variation in patients with coronary heart disease.

(Observational Study)
by two cardiovascular specialists. The data included patients’
disease histories: age, gender, diabetes, hypertension, hyperlipi-
demia, smoking, and laboratory results which included: RDW, 
total cholesterol, high-density lipoprotein cholesterol (HDL-C), 
low-density lipoprotein cholesterol (LDL-C), triglycerides, fast-
ing plasma glucose and clinical indicators (severity of coronary 
disease). For all patients, 3 ml fasting blood was collected from 
the medial cubital vein and stored in Eppendorf tubes. An 
automatic hematology analyzer was used to test RDW, and a 
Hitachi 7170-automatic biochemical analyzer and its correspond-
ing reagents were used to measure fasting plasma glucose, total 
cholesterol, triglycerides, HDL-C, LDL-C and other indicators. 
Based on the RWD grouping method by Özcan et al (2013)10 
cases were divided into three groups (A, B and C, respectively), 
by sorting the RDW values in an ascending order.

Dynamic Electrocardiography

Dynamic electrocardiography was conducted on all study 
participants during hospitalization, and the data were recorded 
using a MDS 300—4A ECG recorder (DMS Corporation, USA). 
The playback recordings were performed by professionals using 
software for advanced dynamic analysis of electrocardiograms by 
Cardioscan Luxury (Tim software (Beijing) Limited). Artifacts or 
interference were eliminated manually, and related data were 
analyzed and calculated. The analysis process strictly followed 
the single-blind principle, whereby the data analyzers were 
blinded to the case grouping, and the clinicians were blinded 
to the data analysis. Diurnal QTc calculations were done auto-
matically by the analysis software, including correction of QT 
intervals using Bazett’s formula (QTc = QTRR). Daytime was set 
from 06:00 to 22:00 and nighttime from 22:00 to 06:00, and the 
diurnal QTc variation of each patient was obtained by subtracting 
mean daytime QTc from mean nighttime QTc.

Coronary Angiography and Interpretation of 
Results

All study participants underwent CAG during hospital-
ization, in which the Seldinger method for radial artery cath-
terization was adopted. The CAG procedure and the evaluation 
of results were performed by two to three cardiovascular 
specialists, and the Gensini grading method was applied to 
assess the severity of coronary artery stenosis and the blood 
vessels involved11 (Table 1)

![Table 1: Gensini Grading Method](https://www.md-journal.com)

| Stenosis Score, % | 1–25 | 26–50 | 51–75 | 76–90 | 91–99 | 100 (fully occluded) |
|------------------|------|-------|-------|-------|-------|---------------------|
| Stenosis Severity Score | 1 | 2 | 4 | 8 | 16 | 32 |
| Location | Left main coronary artery | Left anterior descending or proximal circumflex | Medial left anterior descending | Distal left anterior descending | Medial and distal left circumflex | Right coronary artery |
| Lesion Score | 5 | 2.5 | 1.5 | 1 | 1 | 0.5 |

Score of each lesion was stenosis severity score multiplied by lesion score, and the score of each patient was sum of each item score.

Statistical Analysis

The measurement data were expressed as mean ± standard 
declaration, and measurement data were expressed as frequency or 
percentages. Independent samples t-test was used to compare 
the measurement data between two groups, and variance analysis was 
used for comparison among groups. Fisher’s Least Significant 
Difference and Student–Newman–Keuls tests were used for 
multiple comparisons of mean values. Pearson’s correlation 
analysis was used to analyze correlation of coronary artery score, 
RDW and diurnal QTc variation. Receiver operating character-
istic (ROC) curves were used to determine the optimal threshold 
RDW value for the diagnosis of acute coronary syndrome, and 
areas under ROC curves and 95% confidence intervals (CI) were 
calculated to compare the diagnostic efficiencies. All statistical 
analyses were conducted using SPSS 20.0 software, and P < 0.05 
was considered statistically significant.

RESULTS

Comparison of Baseline Data

By sorting RDW values in an ascending order, the patients 
were divided into three groups, denoted as A, B and C groups. 
The sex ratio, age, blood pressure, blood glucose, blood lipids, 
night QTc and average heartbeat had no significant differences 
among these groups (P > 0.05). However, the RDW value, 
coronary artery score and diurnal QTc variation of these groups 
were significantly different (P < 0.05). The coronary artery 
score (Gensini score) gradually increased with RDW, while 
diurnal QTc variation decreased with RDW value, as illustrated 
in Table 2.

Pearson’s Correlation Analysis

Pearson’s correlation analysis was applied to assess 
possible effects of other factors, and then multiple correlations 
among coronary artery score, RDW, and diurnal QTc variation 
were analyzed. Results showed that the coronary artery score 
was positively correlated with RDW (r = 0.130, P = 0.020) but 
was not correlated with the diurnal QTc variation (r = 0.226, 
P = 0.681), while the RDW was negatively correlated with the 
diurnal QTc variation (r = 0.197, P = 0.035), as shown in 
Figure 1.

Selection of the Best Cutoff Value for RDW in 
Acute Coronary Syndrome Patients

The RDW values in patients with or without acute coron-
ary syndrome were analyzed to determine the predictive value 
of RDW for the diagnosis of acute coronary syndrome. The 
ROCs curves suggest that RDW (area under the curve (AUC) 
0.816 [95% CI 0.752–0.880]) has better sensitivity and speci-
ficity for predicting acute coronary syndrome than diurnal QTc 
variation (AUC 0.570 [95% CI 0.490–0.651]) (Figure 2).

DISCUSSION

In the present study we explored a potential relationship 
between the RDW and the diurnal QTc variations and its utility 
in diagnosing and prognosticating CHD. Validating our dataset, 
we confirmed the previous finding4,12 that the coronary artery 
score was positively correlated with RDW. Several previous 
 studies have shown that the RDW predictor is independent of 
hemoglobin levels, indicating that the poor prognosis of cardio-
vacular disease associated with increased RDW may not be 
related to anemia. The mechanism of RDW elevation in patients
with CHD is still unclear, but was proposed to be related to chronic inflammation, oxidative stress, renal dysfunction, and neuroendocrine system activation.\textsuperscript{13–19} Some studies have suggested that long-term activation of the neuroendocrine system can suppress bone marrow hematopoiesis and result in increased RDW. It was suspected that in CHD patients, increased RDW is associated with myocardial ischemia activating the sympathetic nervous system, which partially reflects the extent of myocardial ischemia. But this theory has not been supported by clinical and laboratory evidence. Recently, Özcan et al\textsuperscript{10} studied the correlation between heart rate variability (HRV) and RDW by conducting 24 h dynamic ECG examination and detecting RDW in blood samples of 180 patients with confirmed systolic heart failure. They found that RDW was independently negatively correlated with parameters of heart rate variability in patients with heart failure, where HRV parameters (SDNN, SDANN, RMSSD) decreased with increase in RDW, suggesting that RDW elevation coincided with autonomic nerve dysfunction.

### Table 2. Baseline Data of the 3 Groups

|                      | Group A: n = 68 | Group B: n = 68 | Group C: n = 67 | P (ANOVA)   |
|----------------------|----------------|----------------|----------------|-------------|
| RDW                  | 11.69 ± 0.579\% | 12.86 ± 0.241\% | 14.06 ± 0.888\% | < 0.001     |
| Male/female          | 42/26          | 44/24          | 44/23          | 0.955       |
| Age, y               | 61.88 ± 8.652  | 59.23 ± 8.585  | 60.82 ± 8.665  | 0.197       |
| Systolic blood pressure, mmHg | 133.76 ± 23.18 | 137.86 ± 19.42 | 138.36 ± 20.60 | 0.382       |
| Diastolic blood pressure, mmHg | 82.38 ± 13.87  | 85.19 ± 16.93  | 82.15 ± 15.57  | 0.445       |
| Low density lipoprotein, mmol/L | 2.60 ± 0.74    | 2.67 ± 0.67    | 2.67 ± 0.83    | 0.856       |
| Triglycerides, mmol/L | 1.74 ± 1.56    | 1.61 ± 0.91    | 1.86 ± 1.05    | 0.497       |
| High density lipoprotein, mmol/L | 1.21 ± 0.28    | 1.25 ± 0.35    | 1.12 ± 0.23    | 0.051       |
| Fasting plasma glucose, mmol/L | 6.41 ± 0.95    | 6.38 ± 2.04    | 6.45 ± 3.52    | 0.091       |
| Total cholesterol, mmol/L | 4.54 ± 0.90    | 4.68 ± 1.02    | 4.59 ± 1.08    | 0.728       |
| Diurnal QTc variation | −0.82 ± 9.43   | −2.66 ± 7.08   | −3.37 ± 9.37   | 0.021       |
| Night QTc variation   | 93.59 ± 31.18  | 105.84 ± 70.89 | 116.02 ± 71.59 | 0.106       |
| Average heart rate, bpm | 67.41 ± 7.94  | 65.39 ± 7.34  | 68.48 ± 9.39  | 0.088       |
| Gensini score (coronary artery score) | 37.68 ± 30.87 | 39.45 ± 33.23 | 43.04 ± 36.42 | 0.036       |

**FIGURE 1.** Correlation between diurnal QTc variation and RDW.

**FIGURE 2.** Receiver operating characteristic curve (ROC) analysis showing that RWD predicts the incidence of coronary heart disease patients.

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Although QTc is normalized for heart rate, it can still reflect the status of autonomic nerve function to a certain extent. Normal individuals exhibit activated sympathetic nerves, weakened vagal nerves, faster heart rate and shorter QTc at daytime. The opposite pattern occurs during the night thus resulting in negative diurnal QTc variation. Myocardial ischemia in patients with coronary artery disease may lead to impaired autonomic nerve function and changes in cardiac ion channel properties, resulting in prolonged duration and increased dispersion of ventricular repolarization, thereby inducing malignant ventricular arrhythmia. Animal experiments and clinical studies have confirmed that diurnal QTc variation in subjects with CHD is more significant than in the healthy population.20–22 The present study showed that increased RDW values were related with the diurnal QTc variation decreased, which was the first reported. We also found that the differences in the night QTc variation among the three groups was not significant, indicating that the increased diurnal QTc variation may be related to increased sympathetic activity during daytime, especially its sudden increase in early morning.23

This retrospective study was conducted to explore the relationship of the RDW and diurnal QTc variation in patients with CHD, and the two indicators were found to be negatively correlated ($r = -0.197, P = 0.035$). With increased RDW values, the diurnal QTc variation decreased, indicating that increased RDW may be accompanied by autonomic nerve dysfunction in these patients.

After controlling the effects of other factors, Pearson’s correlation analysis showed that there was no correlation between coronary artery score and diurnal QTc variation ($r = -0.226, P = 0.681$), indicating that there could be more complex mechanisms governing the severity of coronary stenosis and autonomic nerve dysfunction. Limitations of this retrospective study include lack of repeated RDW data collection, possible errors in QTc measurement, and the relatively small sample size. This is the first report of a correlation between RDW and diurnal QTc variation, and further clinical and basic studies are required to substantiate this finding.

CONCLUSIONS

In conclusion, increased RDW is independently associated with diurnal QTc variation in patients with CHD. An easily obtained, cheap RDW test may aid in the diagnosis and prognostic assessment of CHD.

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