Usefulness of Red Blood Cell Distribution Width in the Assessment of Hemodynamics After Tetralogy of Fallot Repair

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Background: There are no reports on the effect of red blood cell distribution width (RDW) in surgical repair of tetralogy of Fallot (ToF).

Methods and Results: A total of 50 patients who underwent cardiac catheterization after surgical repair of ToF were retrospectively assessed. RDW was positively correlated with the ratio of right ventricular pressure to left ventricular pressure (RVP/LVP; P<0.0001, r²=0.57). Patients with elevated RDW had a higher RVP/LVP than those with a normal RDW (P<0.0001). Also, elevated RDW was assessed. RDW was positively correlated with the ratio of right ventricular pressure to left ventricular pressure (RVP/LVP; P<0.0001, r²=0.57). Patients with elevated RDW had a higher RVP/LVP than those with a normal RDW (P<0.0001). Also, elevated RDW was related to elevated central venous pressure (P<0.0001), decreased mixed venous oxygen saturation (P<0.0001), greater pulmonary stenosis (P=0.003) and severe pulmonary regurgitation on echocardiography (P<0.0001), a higher rate of residual ventricular septal defect leak (P=0.004) and higher reoperation rate (P=0.009). Of the 7 patients who underwent reoperation, 6 had decrease in RDW after reoperation (P=0.012). On multivariable regression analysis, RDW was the strongest indicator of higher RVP/LVP.

Conclusions: For the first time, RDW has been shown to be a strong indicator for assessing the hemodynamics and risk of later reoperation after surgical repair of ToF.

Key Words: Red blood cell distribution width; Reoperation; Right ventricular pressure; Tetralogy of Fallot

Red blood cell distribution width (RDW) is a quantitative measure of the variability in the size of circulating erythrocytes and is routinely reported as part of the complete blood count. Clinically, RDW is often used in the differential diagnosis of anemia. Also, elevated RDW is a sign of a nutritional deficiency such as a vitamin B12 or folic acid deficiency or recent blood transfusion. Recently, there have been many reports of the association between RDW and heart failure, coronary artery disease, myocardial infarction, pulmonary hypertension, and congenital heart disease. In the previous study, we reported on the usefulness of RDW as a prognostic and convenient marker for detecting heart failure in a Fontan circulation. At present, brain natriuretic peptide (BNP) is regarded as a sensitive prognostic marker in pediatric heart failure. BNP is secreted by the ventricles in response to a volume and pressure load. In patients with surgically repaired ToF, BNP is increased in association with right ventricular (RV) enlargement. The usefulness of BNP in the assessment of hemodynamics after surgical repair of ToF, however, was investigated only for the relatively long-term period after surgical repair in the previous reports. In contrast, although there are increasing reports of the association between RDW and various cardiac conditions, the relationship between RDW and hemodynamics after surgical ToF repair has not been previously reported. Also, there are limited reports on the assessment of short-term hemodynamics after surgical ToF repair. Therefore, we hypothesized that RDW may be associated with the hemodynamics after surgical ToF repair. In this study we retrospectively reviewed the cardiac catheterization data in patients who underwent surgical ToF repair at International Medical Center, Saitama Medical University, and investigated the usefulness of RDW as a marker of the hemodynamics in these patients.

Methods

Patients and Sample Collection
This study was approved by the Institutional Review Board of Saitama Medical University (No. 17-265) and all participants gave informed consent. This study involved 50 consecutive patients who were admitted to the International Medical Center, Saitama Medical University to undergo postoperative cardiac catheterization after surgical ToF repair between June 2011 and December 2017. We routinely perform cardiac catheterization after surgical ToF repair to assess the postoperative hemodynamics. We retrospectively reviewed the demographic data including...
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Table 1. Baseline Characteristics

|                       | RDW <14.5% (n=31) | RDW ≥14.5% (n=19) | P-value |
|-----------------------|-------------------|-------------------|---------|
| Male                  | 17                | 13                | 0.387   |
| Age at surgical repair (months) | 6.8±0.4          | 6.3±0.5           | 0.436   |
| Age at cardiac catheterization (months) | 17.8±1.8         | 18.1±2.6          | 0.915   |
| Time from surgical repair (months) | 11.0±1.6         | 11.8±2.4          | 0.773   |
| Type of surgical repair |                   |                   | 0.559   |
| Transannular patch     | 16                | 12                |         |
| Spared pulmonary valve | 15                | 7                 |         |
| Previous palliative shunt | 9                | 3                 | 0.332   |
| Residual VSD leak      | 2                 | 8                 | 0.004   |
| Cardiotoracic rate (%) | 52.8±0.6          | 54.9±1.2          | 0.097   |
| QRS duration (s)       | 0.112±0.04        | 0.113±0.05        | 0.894   |
| BNP (pg/mL)            | 36.9±0.6          | 58.1±11.1         | 0.085   |
| Hemoglobin (g/dL)      | 12.9±0.1          | 12.6±0.2          | 0.24    |
| Serum albumin (g/dL)   | 4.8±0.05          | 4.7±0.08          | 0.808   |
| Serum creatinine (mg/dL)| 0.25±0.01        | 0.24±0.01         | 0.867   |
| C-reactive protein (mg/dL)| 0.14±0.04     | 0.20±0.11         | 0.513   |
| Reoperation            | 1                 | 6                 | 0.009   |

Data given as n or as mean±SD. BNP, brain natriuretic peptide; LVP, left ventricular pressure; RDW, red blood cell distribution width; RVP, right ventricular pressure; VSD, ventricular septal defect.

Statistical Analysis

All continuous data are expressed as mean±SD. Categorical data were analyzed using Pearson’s chi-squared test or Fisher’s exact test. Comparisons between the 2 groups was performed with Mann-Whitney U-test. Comparisons within groups were made using ANOVA. Pearson’s correlation analysis was used to assess the relationships between RDW and catheterization parameters. Multivariate regression analysis was also performed to determine the independent effect of RDW. P<0.05 was considered statistically significant. All statistical analysis was performed using JMP version 11.2.0 (SAS, Cary, NC, USA) and GraphPad PRISM version 5.01 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline Characteristics

A total of 50 consecutive patients were included in the study. Mean age at the time of surgical repair was 6.6±2.1 months (range, 3–12 months). Of the 50 patients, more than half (56%) underwent transannular patch as the surgical procedure. Cardiac catheterization was performed 11.3±9.6 months after surgical repair. Twelve patients underwent previous palliative shunt (Blalock-Taussig shunt). Also, 10 patients had residual VSD leak after surgical repair. Qp/Qs in these patients was 1.20±0.04. Mean RDW and BNP were 36.9±0.6 and 58.1±11.1 mg/dL, respectively. Mean RVP/LVP at the time of cardiac catheterization was 0.54±0.16. Almost half of the patients had mild pulmonary regurgitation on echocardiography. In contrast, 24% of the patients had severe pulmonary regurgitation. Mean QRS duration on ECG at the time of admission was 0.113±0.02 s. A total of 7 patients underwent reoperation after cardiac catheterization. The indications for reoperation were significant VSD leak (n=4) and pulmonary stenosis (n=3). Of the 7 patients who underwent reoperation, Qp/Qs in the 4 patients with residual VSD leak was 1.27, 1.32, 1.30 and 1.50, respectively; and the...
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r²=0.587; Figure 1A. RVP/LVP was significantly higher in the elevated RDW group than the normal RDW group (0.71±0.03 and 0.44±0.01, respectively, P<0.0001; Figure 1B). In contrast, CI was equivalent between the 2 groups.

The relationship between RDW and severity of pulmonary regurgitation and pulmonary stenosis on echocardiography was also assessed. Patients with severe pulmonary regurgitation (ratio of proximal color Doppler jet width relative to pulmonary valve annulus diameter >0.5) had a significantly higher RDW than the patients with mild or moderate pulmonary regurgitation (Figure 2). Also, the severity of pulmonary stenosis was greater in the elevated RDW group than the normal RDW group (22.9±3.8 mmHg and 11.9±1.6 mmHg, respectively, P=0.003).

Table 2. Catheterization and Echocardiography vs. RDW Level

| RDW <14.5% | RDW ≥14.5% | P-value |
|------------|------------|---------|
| Cardiac index | 3.90±0.19 | 4.28±0.18 | 0.174 |
| CVP (mmHg) | 5.5±0.4 | 8.5±0.3 | <0.0001 |
| SvO2 (%) | 77.0±1.2 | 67.9±1.1 | <0.0001 |
| RVP/LVP ratio | 0.44±0.01 | 0.71±0.03 | <0.0001 |
| EF (%) | 71.8±1.6 | 68.5±1.9 | 0.208 |

**Pulmonary regurgitation**

|        | RDW <14.5% | RDW ≥14.5% | P-value |
|--------|------------|------------|---------|
| Mild   | 17 | 7 | 0.255 |
| Moderate | 10 | 4 | 0.522 |
| Severe | 4 | 8 | 0.038 |

**Pulmonary stenosis (mmHg)**

|        | RDW <14.5% | RDW ≥14.5% | P-value |
|--------|------------|------------|---------|
|        | 11.9±1.6 | 22.9±3.8 | 0.003 |

*Data given as n or as mean ± SD. CVP, central venous pressure; EF, ejection fraction; SvO2, mixed venous oxygen saturation. Other abbreviations as in Table 1.*
RDW After ToF Repair

After surgical ToF repair, because it correlates with RV volume load. In contrast, 1 patient did not have a decrease in RDW. The RDW level in that patient was within normal limits before reoperation (RDW, 13.2%). Finally, receiver operating characteristic curve analysis was carried out for the discrimination of reoperation. RDW >15.15 could detect reoperation with 71.4% sensitivity and 90.7% specificity (Figure 4).

Assessment of BNP
We assessed BNP and other parameters as a related factor in the same manner. There was a positive correlation between BNP and RVP/LVP (P=0.02, r²=0.11). Also, BNP had a weak negative correlation with SvO₂ (r²=0.1, P=0.02). BNP, however, was not associated with CI or CVP. Furthermore, although patients with elevated BNP tended to have a higher rate of reoperation compared with the patients with normal BNP, this was not significant (P=0.062).

Regarding the other parameters, there was a positive correlation between cardiothoracic ratio on chest X-ray and RVP/LVP (P=0.003). Age at the time of surgical repair and QRS duration on ECG were not associated with higher RVP/LVP or reoperation rate.

Multivariable Regression Analysis
Multivariable regression analysis was performed to assess whether RDW was an independent and the strongest factor to predict higher RVP/LVP after the surgical repair of ToF. On multivariate regression analysis including RDW, BNP, cardiothoracic ratio, degree of pulmonary stenosis and severity of pulmonary regurgitation, which might affect higher RVP/LVP ratio, RDW and degree of pulmonary stenosis were independent predictors of elevated RVP/LVP, and RDW was the strongest indicator of elevated RVP/LVP (β-coefficient, 0.09; SE, 0.011; P<0.0001).

Discussion
ToF is the most common cyanotic congenital heart disease and there are many studies on the short-term and long-term surgical results, sequelae after intracardiac surgery, and postoperative hemodynamic assessment. Clinically, BNP is regarded as one of the markers of hemodynamics after surgical ToF repair, because it correlates with RV volume load. Similarly, a longer QRS duration on ECG and severe pulmonary regurgitation on echocardiography are regarded as prognostic parameters that lead to ventricular arrhythmias or sudden death in the long term.

In the present study, we found that elevated RDW correlated with higher RVP/LVP, higher CVP and lower SvO₂, suggesting an excessive volume overload and pressure overload on the RV and low cardiac status. Also, the patients with residual VSD leak had a higher RDW compared with those without VSD leak. And the patients with severe pulmonary regurgitation had a higher RDW compared with those with mild or moderate pulmonary regurgitation. This suggests that RDW is a sensitive marker in detecting volume overloads in the cardiac chamber after surgical ToF repair. With regard to this point, the present results confirm the previous reports that RDW reflects excessive volume overload in the cardiac chamber in heart failure patients. Moreover, the fact that the elevated RDW...
group had greater pulmonary stenosis suggests that higher RDW may reflect not only volume overload but also excessive pressure overload in the cardiac chamber after surgical ToF repair, which was not discussed in the previous reports.

Although BNP is a good marker after ToF repair, RDW was as strong an indicator as BNP and a more convenient marker than BNP. In the present study, RDW was the strongest indicator of higher RVP/LVP on multivariable regression analysis. In contrast, cardiothoracic rate on chest X-ray was also correlated with higher RVP/LVP. This was not surprising because larger cardiothoracic rate on chest X-ray may indicate excessive volume overload in the cardiac chamber.

Also, the elevated RDW group had a higher reoperation rate than the normal RDW group in this study. Most of these patients underwent reconstruction of the RV outflow tract or closure of the residual VSD shunt to release the pressure and volume overload of the RV. We found that RDW >15.15 could identify, with 71.4% sensitivity and 90.7% specificity, reoperation afterwards. Therefore, we speculated that elevated RDW may be a novel indicator of risk for reoperation after surgical ToF repair in the short term. In the present study, RDW ≥14.5% was an indicator of risk of deterioration of hemodynamic status after surgical ToF repair. These include higher RVP/LVP, pulmonary stenosis, severe pulmonary regurgitation, residual VSD leak, higher CVP and lower SvO2. Moreover, RDW ≥15.15% indicates a risk of reoperation afterwards. Therefore, we regard RDW 14.5–15.15% as indicative of hemodynamic deterioration, and RDW ≥15.15% as indicating a high risk of reoperation after surgical ToF repair. Also, we found that RDW decreases after reoperation. Of the 7 patients who underwent reoperation, 6 patients had decrease in RDW afterwards. In these patients, RDW decreased from 15.4±0.2 to 13.3±0.3. This suggests that RDW may reflect hemodynamic change before and after surgical repair of ToF.

In the present study, we could not find a relationship between QRS duration and postoperative hemodynamics. This may have been due to the short study period between the surgery and cardiac catheterization. Although QRS duration is predictive of ventricular tachycardia and sudden death in the long term, the ECG findings may not be significant in the short term after surgical repair, especially in small infants. Similarly, higher age at the time of surgical repair is regarded as a risk factor for high mortality. In the present study, however, because the age at the time of surgical repair was relatively low, we could not find any relationship between age at the time of surgical repair and other parameters.

Over the past 10 years, there have been many reports indicating that RDW is a strong prognostic marker in the assessment of acute and chronic heart failure, myocardial infarction, and pulmonary hypertension. RDW is recognized as a convenient and useful prognostic marker in various cardiac conditions and diseases. Nevertheless, there was limited information regarding the efficacy of RDW in congenital heart disease. Nowadays, several methods including echocardiography, BNP, and cardiac catheterization, are available to assess the hemodynamics after surgical ToF repair. In addition to these indexes, RDW may become a useful and convenient marker in the assessment of the hemodynamics after surgical ToF repair. Because RDW is automatically reported as part of the complete blood count, it is more convenient and cost-effective than BNP. Also, unlike echocardiography, there is no inter- or intra-examiner discrepancy. To the best of our knowledge, this is the first report to assess the relationship between RDW and hemodynamics after surgical ToF repair in the short term.

RDW reflects the variability in the size of the circulating red blood cells and is routinely reported in the automated assessment of complete blood counts. Because of its convenience, one can check its transition frequently compared with other biomarkers, such as BNP. RDW is often used in the differential diagnosis of anemia, and elevation in RDW is seen in conditions of ineffective red cell production or after blood transfusions. The precise mechanism by which elevated RDW was associated with higher RVP/LVP in this study is unknown. RDW may represent a variety of mechanisms including inflammatory stress, nutritional deficiency, and inadequate production of erythropoietin, which is associated with heart failure. Pro-inflammatory cytokines have been found to inhibit erythropoietin-induced erythrocyte maturation, which is reflected in part by an increase in RDW. These mechanisms may apply to the hemodynamic changes after surgical ToF repair, although we do not have sufficient supportive data.

This study had some limitations to be noted. First, because the study was relatively small and retrospective, the findings need to be confirmed in a larger, prospective study. Second, catheterization data in the present study were relatively limited to the right heart, and one can speculate that the results of right heart catheterization data including CVP, SvO2 and RVP interact with each other. This may be another limitation. Third, the long-term effect of RDW as a prognostic marker after surgical ToF repair is unclear, because the present study was limited to the short term. The long-term effect of RDW needs to be elucidated in a future study. Finally, there are no data on the normal range of RDW in small infants. Therefore, we used the normal range of RDW in adults.

Conclusions

For the first time, RDW has been shown to be a strong indicator of hemodynamics after surgical ToF repair in the short term. Also, RDW was a sensitive indicator of the risk of reoperation afterwards. Because of its sensitivity and convenience, RDW may become a novel marker in the assessment of hemodynamics after surgical ToF repair.

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Disclosures

The authors declare no conflicts of interest.

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