International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Red cell distribution width in adults with congenital heart disease: A worldwide available and low-cost predictor of cardiovascular events☆

Vivan J.M. Baggen [a,b], Annemien E. van den Bosch [a], Roland R. van Kimmenade [c,d], Jannet A. Eindhoven [a], Maarten Witsenburg [a], Judith A.A.E. Cuypers [a], Frank W.G. Leebeek [e], Eric Boersma [a,b,f], Jolien W. Roos-Hesselink [a,*]

[a] Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands
[b] Cardiovascular Research School COEUR, Rotterdam, The Netherlands
[c] Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands
[d] Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands
[e] Department of Hematology, Erasmus Medical Center, Rotterdam, The Netherlands
[f] Department of Clinical Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 26 June 2017
Received in revised form 11 February 2018
Accepted 28 February 2018
Available online xxxx

Keywords:
Red cell distribution width
Biomarker
Prognosis
Risk
Adult congenital heart disease

ABSTRACT

Background: Red cell distribution width (RDW) is a standard component of the automated blood count, and is of prognostic value in heart failure and coronary heart disease. We investigated the association between RDW and cardiovascular events in patients with adult congenital heart disease (ACHD).

Methods and results: In this prospective cohort study, 602 consecutive patients with ACHD who routinely visited the outpatient clinic were enrolled between 2011 and 2013. RDW was measured in fresh venous blood samples at inclusion in 592 patients (median age 33 [IQR 25–41] years, 58% male, 90% NYHA I) and at four annual follow-up visits. During 4.3 [IQR 3.8–4.7] years of follow-up, the primary endpoint (death, heart failure, hospitalization, arrhythmia, thromboembolic events, cardiac intervention) occurred in 196 patients (33%). Median RDW was 13.4 (12.8–14.1)% versus 12.9 (12.5–13.4)% in patients with and without the primary endpoint ($P < 0.001$). RDW was significantly associated with the endpoint when adjusted for age, sex, clinical risk factors, CRP, and NT-proBNP (HR 1.20; 95% CI 1.06–1.35; $P = 0.003$). The C-index of the model including RDW was slightly, but significantly ($P = 0.005$) higher than the model without (0.74, 95% CI 0.70–0.78 versus 0.73, 95% CI 0.69–0.78). Analysis of repeated RDW measurements (n = 2449) did not show an increase in RDW prior to the occurrence of the endpoint.

Conclusions: RDW is associated with cardiovascular events in patients with ACHD, independently of age, sex, clinical risk factors, CRP, and NT-proBNP. This readily available biomarker could therefore be considered as an additive biomarker for risk stratification in these patients.

1. Introduction

Red cell distribution width (RDW) is a marker of anisocytosis, which is automatically measured when a complete blood count is requested. RDW is calculated as the coefficient of variation of the red cell volume distribution (standard deviation divided by mean cell volume). A high RDW indicates a greater variation in erythrocyte size, and a low RDW indicates a more homogeneous population of red blood cells [1]. Various distinct pathophysiological mechanisms such as impaired iron mobilization, ineffective erythropoiesis, nutritional deficiencies, decreased hemoglobin level, oxidative stress, and inflammation have been related to an increased RDW [2–5].

Interestingly, increased RDW has been reported to be closely related to the risk of adverse events in the general population [6,7]. More specific, it has been shown to be a predictor of cardiovascular morbidity and mortality in patients with acute and chronic heart failure [2,8–11], coronary heart disease [12,13] and pulmonary arterial hypertension [14]. Even an increase in RDW during hospitalization has been related to adverse outcome [15]. Despite these promising data, its current role in clinical practice still pertains to the differential diagnosis of anemia together with the mean cell volume, which was already described in 1983 [16,17].

The number of patients with adult congenital heart disease (ACHD) is rapidly increasing and although many of these patients have no

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Erasmus University Medical Center, Department of Cardiology, Room Ba-583a, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands.
E-mail address: j.roos@erasmusmc.nl (J.W. Roos-Hesselink).

https://doi.org/10.1016/j.ijcard.2018.02.118

complaints, the incidence of cardiovascular events and need for (re)interventions is high. Prognostication is an essential component of the routine clinical care of patients with ACHD, and forms the basis of patient information, follow-up management and therapeutic strategies. To our knowledge, it is unknown whether RDW can enhance the prognostication of ACHD patients. The aim of this study was therefore to investigate the association between RDW and cardiovascular events in patients with ACHD. In addition, we evaluated repeated measurements to investigate the changes in RDW level over time.

2. Methods

2.1. Study design and population

This is a prospective cohort study. We included consecutive adults with a moderate or complex type of congenital heart defect [18], who routinely visited our ACHD outpatient clinic with an echocardiogram between April 2011 and April 2013. We excluded patients with age < 18 years, pregnancy, a mild cardiac lesion (isolated atrial or ventricular septal defect), not capable of understanding and signing informed consent, or severe kidney disease (estimated glomerular filtration rate < 30 mL/min at baseline). At the day of study inclusion, patients underwent physical examination by a cardiologist, 12-lead electrocardiography, echocardiography and venous blood sampling. All patients were structurally followed-up during four years by annual visits to the ACHD outpatient clinic, including physical examination by a cardiologist, 12-lead electrocardiography, venous blood sampling, and echocardiography (every two years). During the follow-up, patients were treated in accordance with ESC guidelines [19].The study protocol was approved by the Erasmus MC medical ethics committee and all participants provided written informed consent. Other details of the study protocol and the echocardiographic image analysis have been described previously [20,21].

2.2. Laboratory measurements

An automated complete blood count was performed in fresh K2EDTA plasma samples at study inclusion and at the planned yearly follow-up visits in the clinical chemistry laboratory of the Erasmus MC, using a Sysmex XN-1000™ Hematology Analyzer (Sysmex Europe GmbH, Norderstedt, Germany). Up to five subsequent annual measurements per patient were collected. Samples were stored at room temperature and were analyzed within 3 h of collection. RDW measurements were performed for research purposes only, and decisions regarding patient management were made independently of RDW measurements. The lower and upper limits of normal for RDW in our lab are 12.0 and 16.0%, respectively. Anemia was defined as a hemoglobin level of <139 g/L in men (<8.6 mmol/L) and <121 g/L (<7.5 mmol/L) in women. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was directly measured in fresh serum samples, using a commercial electrochemiluminescence immunoassay (Roche Diagnostics, Rotkreuz, Switzerland). More details have been published previously [21].

2.3. Definition and assessment of events

We defined the primary endpoint prior to the collection of data as a composite of the following (cardiovascular) events: all-cause mortality, heart failure (requiring initiation or change in heart failure medication, or requiring hospital admission), hospitalization for cardiac reasons, arrhythmia (symptomatic and recorded, or requiring treatment), thromboembolic events (ischemic cerebrovascular accident, pulmonary embolism or myocardial infarction), and/or cardiac interventions (surgical or percutaneous). The secondary endpoint was defined as a composite of all-cause mortality and/or heart failure.

According to the study protocol, patients were followed for the occurrence of fatal and non-fatal events by a yearly clinical evaluation at our institution. The end of the follow-up period was set on August 1, 2016. Survival status was also checked in the Municipal Population Register. Suspect endpoint events were adjudicated by two experienced investigators (VB and JR) without knowledge of RDW levels.

2.4. Statistical analysis

Patient characteristics were described per quartile of the RDW distribution. Depending on the data distribution, these were presented as mean ± standard deviation or as median [interquartile range (IQR)]. Comparisons across quartiles of the RDW distribution were performed using the Chi-Square Mantel-Haenszel test for trend (for categorical variables) or linear regression (for continuous variables).

For patients with multiple events, event-free survival was defined as the time from enrollment to the occurrence of the first event. Patients without any cardiovascular event were censored at the end of the follow-up duration. Kaplan-Meier endpoint-free survival curves were presented for each RDW quartile separately. Cox regression was performed to investigate the association between baseline RDW and study endpoints. We analyzed RDW both as a categorical variable (in quartiles) and as a continuous variable (RDW was normally distributed and presented per % increase). We also investigated the association of the other components of the automated blood count (hemoglobin, hematocrit and mean cell volume) with the primary and secondary endpoint. Associations were adjusted for age, sex, congenital diagnosis, cardiac medication use, NYHA class, rhythm, and systemic ventricular function. Furthermore, we performed additional adjustment for C-reactive protein and NT-proBNP. Data on NT-proBNP was 99% complete; imputation of the mean was used to account for missing data. All other covariates were 100% complete. We reported crude and adjusted hazard ratios (HR) and their corresponding 95% confidence intervals (CI).

In order to evaluate the potential added value of RDW for risk prediction, we determined C-statistics of models with and without RDW as a predictor. Models were compared using the likelihood ratio test [22].

We developed linear mixed-effects (LME) models to analyze the temporal pattern of RDW throughout the follow-up, while accounting for the correlation between subsequent RDW measurements within individuals. The correlations in the repeated RDW measurements were modeled using a random intercept and a linear random slopes term. Within-subject variation was expressed as residual variance / total variance * 100%. Between-subject variation calculated as (total variance − residual variance) / total variance * 100%. We evaluated differences in temporal evolvement of RDW between patients with and without the study endpoints by LME models including a time * endpoint interaction term in the fixed part of the model. Because the temporal RDW evolution was similar in patients with and without study endpoints, we did not apply joint modeling to obtain hazard ratios for these relations.

Data analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) and using the survC1, nlme and JMBayes packages in R statistical software, version 3.3.2 (available at: www.r-project.org) [23,24]. Two-sided *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Study cohort

Of the 602 patients with moderate to complex ACHD who were included in the cohort, a baseline RDW measurement was available in 592 patients. None of the patients had to be excluded because of severe kidney disease at baseline. The median age at inclusion was 33 [IQR 25–41] years and 342 (58%) were male. Surgical repair was performed in 537 patients (91%) at young age (3.8 [IQR 0.8–11.9] years). The majority of patients were in NYHA class I (90%). Anemia was present in 28 patients (5%). Other baseline characteristics are described in Table 1.

3.2. Association of RDW with patient characteristics

Median RDW was 13.1 [IQR 12.7–13.7, range 11.3–20.7]%. The majority of baseline RDW measurements was within the normal range: only 17 patients (3%) had a RDW <12.0% and only 15 patients (3%) had a RDW >16.0%. In the highest RDW quartile, patients were significantly older and underwent surgical repair at an older age. Moreover, a larger proportion was female, had a complex congenital diagnosis, used cardiac medication, had a low oxygen saturation and was in NYHA class II-III. In addition, in the highest RDW quartile a larger proportion of patients had loss of sinus rhythm, and patients had a worse systemic ventricular function and higher NT-proBNP levels. Baseline characteristics across quartiles of RDW distribution are further detailed in Table 1. RDW levels were higher in patients with pulmonary hypertension, a functionally univenticular heart or a congenitally corrected transposition of the great arteries (Supplemental File 1).

3.3. Follow-up

Survival status according to the Municipal Population Register and detailed follow-up data regarding non-fatal events were available in 588 patients (99.3%). After a median of 4.3 [3.8–4.7] years of prospective follow-up, the primary endpoint occurred in 196 patients (33%) and the secondary endpoint occurred in 57 patients (10%). The components of the primary endpoint are separately displayed in Table 2.

3.4. Relation between baseline RDW and study endpoints

Median RDW was 13.4 (12.8–14.1)% versus 12.9 (12.5–13.4)% in patients with and without the primary endpoint, respectively ($P < 0.001$). Median RDW was 13.9 (13.4–15.0)% versus 12.9 (12.5–13.5)% in patients with and without the secondary endpoint, respectively

Please cite this article as: V.J.M. Baggen, et al., Red cell distribution width in adults with congenital heart disease: A worldwide available and low-cost predictor of cardiovascular events, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.02.118