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

Table 1
Baseline characteristics of the study population.

		Baseline RDW quartiles (n = 592)				
	All (n = 592)	Q1 (<12.7%, n = 173)	Q2 (12.7–13.1%, n = 137)	Q3 (13.1–13.7%, n = 149)	Q4 (≥13.7%, n = 133)	*P* for trend
Clinical characteristics						
Age, years	33 [25–41]	31 [24–39]	30 [23–39]	33 [26–45]	37 [28–48]	<0.001
Sex, male, n (%)	342 (58)	112 (65)	85 (62)	88 (59)	57 (43)	<0.001
Surgical repair, n (%)	537 (91)	156 (90)	123 (90)	133 (89)	125 (94)	0.349
Age at surgical repair, years	3.8 [0.8–11.9]	1.9 [0.5–9.2]	2.8 [0.5–11.7]	4.2 [1.2–12.8]	7.4 [2.6–17.8]	<0.001
Congenital diagnosis, n (%)[a]	318 (54)	90 (52)	57 (42)	83 (56)	88 (66)	0.004
Cardiac medication use, n (%)	211 (36)	36 (21)	35 (26)	65 (44)	75 (56)	<0.001
Body mass index, kg/m^2	24.8 ± 4.4	24.1 ± 3.7	24.8 ± 4.2	24.6 ± 4.3	25.8 ± 5.2	0.001
Heart rate, beats/min	74 ± 13	73 ± 14	73 ± 13	73 ± 13	75 ± 13	0.165
Systolic blood pressure, mm Hg	126 ± 16	127 ± 15	126 ± 15	126 ± 15	126 ± 20	0.619
O_2 saturation < 90%, n (%)	17 (3)	2 (1)	0 (0)	1 (1)	14 (11)	<0.001
NYHA class, II-III, n (%)	59 (10)	7 (4)	4 (3)	17 (11)	31 (23)	<0.001
Electrocardiogram						
Rhythm, n (%)						<0.001
Sinus rhythm	514 (87)	161 (93)	125 (91)	123 (83)	105 (79)	
Paced rhythm	43 (7)	6 (3)	6 (4)	17 (11)	14 (11)	
Other	35 (6)	6 (3)	6 (4)	9 (6)	14 (11)	
QRS duration, ms	112 [99–137]	112 [102–137]	106 [96–126]	114 [100–147]	118 [98–141]	0.205
Echocardiogram						
LA volume, mL/m^2[b]	21 [16–29]	20 [14–27]	20 [15–30]	21 [15–28]	24 [19–40]	<0.001
LV end-diastolic volume, mL/m^2[b]	64 ± 19	63 ± 16	65 ± 18	62 ± 19	63 ± 22	0.733
LV ejection fraction, %[b]	56 ± 8	57 ± 6	56 ± 8	56 ± 8	55 ± 10	0.119
RV end-diastolic annulus, mm	42 ± 8	42 ± 8	41 ± 8	42 ± 9	44 ± 9	0.104
RV fractional area change, %	38 ± 11	39 ± 11	38 ± 11	38 ± 12	37 ± 13	0.338
Systemic ventricular function, n (%)						<0.001
Normal	299 (51)	94 (54)	81 (59)	66 (44)	58 (44)	
Mildly impaired	208 (35)	63 (36)	39 (28)	58 (39)	48 (36)	
Moderately impaired	67 (11)	15 (9)	15 (11)	17 (11)	20 (15)	
Severely impaired	18 (3)	1 (1)	2 (2)	8 (5)	7 (5)	
E/A ratio	1.6 ± 0.7	1.8 ± 0.7	1.7 ± 0.7	1.5 ± 0.6	1.5 ± 0.6	0.001
E' wave, cm/s	8.3 ± 2.7	8.8 ± 2.8	8.6 ± 2.7	8.1 ± 2.4	7.2 ± 2.5	<0.001
E/E' ratio	11.6 ± 5.1	11.1 ± 4.4	10.8 ± 4.8	11.3 ± 4.2	13.7 ± 6.7	0.001
Laboratory results						
Hemoglobin, g/L[c]	149 ± 16	151 ± 11	149 ± 12	149 ± 14	145 ± 24	0.003
Hematocrit, L/L	0.44 ± 0.04	0.44 ± 0.03	0.44 ± 0.03	0.44 ± 0.03	0.44 ± 0.06	0.381
Mean cell volume, fL	88 ± 5	88 ± 4	88 ± 4	88 ± 4	87 ± 7	0.077
Creatinine, μmol/L	77 ± 18	77 ± 13	77 ± 15	75 ± 14	79 ± 28	0.432
eGFR, mL/min	90 [82–90]	90 [85–90]	90 [84–90]	90 [82–90]	87 [75–90]	<0.001
C-reactive protein, mg/L	1.5 [0.6–3.5]	1.0 [0.5–2.5]	1.3 [0.5–3.3]	1.3 [0.5–3.4]	2.5 [1.3–6.3]	<0.001
Total cholesterol, mmol/L	4.8 ± 1.0	4.6 ± 0.9	4.8 ± 0.9	4.9 ± 1.1	4.8 ± 1.1	0.050
Low density lipoprotein, mmol/L	3.0 ± 0.9	2.8 ± 0.8	3.0 ± 0.8	3.1 ± 1.0	3.0 ± 1.0	0.032
NT-proBNP, pmol/L	15.0 [6.8–33.4]	10.1 [5.5–21.7]	11.7 [5.2–27.3]	16.6 [7.9–31.3]	31.1 [11.9–70.8]	<0.001

Legend: Values are reported as median [IQR], otherwise as n (%) or mean ± SD. Differences across baseline RDW quartiles are analyzed using the Chi-Square Mantel-Haenszel test for categorical variables, otherwise using linear regression.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RDW, Red blood cell distribution width; RV, right ventricular.

[a] Congenital diagnosis of aortic stenosis, aortic coarctation or arterial switch operation (0) versus tetralogy of Fallot, Rastelli, systemic RV, univentricular heart or pulmonary arterial hypertension [1].

[b] Left sided volumes were not measured in patients with a systemic right ventricle, functionally univentricular heart, pulmonary hypertension (n = 137) or a poor acoustic window.

[c] Hemoglobin was converted from mmol/L to g/L by using the conversion factor 0.06202.

($P < 0.001$). The cumulative RDW distribution in patients with and without study endpoints is depicted in Supplemental File 2.

Patients who were in a higher RDW quartile had a significantly lower primary and secondary endpoint-free survival, as is shown in the Kaplan-Meier curves in Fig. 1. When the RDW quartiles were analyzed in a multivariable Cox model including multiple clinical variables, C-reactive protein, and NT-proBNP, the association was partially attenuated but remained statistically significant. Moreover, each separate component of the primary endpoint seemed to occur more frequently in patients in the highest RDW quartile (Table 2). As is shown in Table 3, similar conclusions were found when RDW was analyzed as a continuous variable. None of the other components of the automated blood count (hemoglobin, hematocrit and mean cell volume) were predictive of the primary endpoint; however, a decreased hemoglobin was significantly associated with the secondary endpoint. We therefore conducted sensitivity analyses with additional adjustment of the associations between RDW and study endpoints for hemoglobin, which did not yield different conclusions.

A basic risk marker model including age, sex, congenital diagnosis, cardiac medication use, NYHA class, rhythm, systemic ventricular function, and NT-proBNP yielded a C-index of 0.73 (95% CI 0.69–0.78) for the primary endpoint. The augmented model with RDW included as predictor yielded a C-index of 0.74 (95% CI 0.70–0.78), which was a modest but significant improvement ($P = 0.005$).

3.5. Repeated RDW measurements

During the follow-up, a total of 2449 RDW measurements were collected. Although the majority of the RDW measurements (n = 2085, 85%) were in the normal range, the RDW was clearly and consequently higher at baseline and throughout the entire follow-up duration in patients with a primary endpoint, compared with patients who remained

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

Table 2
Risk of the primary composite endpoint (cardiovascular event) and secondary composite endpoint (death or heart failure) according to baseline RDW quartiles.

		RDW quartiles (n = 592)				
	All (n = 592)	Q1 (<12.7%, n = 173)	Q2 (12.7–13.1%, n = 137)	Q3 (13.1–13.7%, n = 149)	Q4 (≥13.7%, n = 133)	*P* for trend[a]
Cardiovascular event						
No. Cases	196	34	34	55	73	
Person-years	1966	620	504	473	369	
Crude HR (95% CI)		Reference	1.24 (0.77–1.99)	2.10 (1.37–3.22)	3.48 (2.32–5.23)	<0.001
Adjusted HR (95% CI)[b]		Reference	1.23 (0.77–1.99)	1.49 (0.99–2.32)	2.13 (1.38–3.30)	<0.001
Adjusted HR (95% CI)[c]		Reference	1.14 (0.71–1.84)	1.44 (0.92–2.24)	1.76 (1.12–2.76)	0.009
Death or heart failure						
No. Cases	57	3	4	14	36	
Person-years	2338	690	585	590	472	
Crude HR (95% CI)		Reference	1.61 (0.36–7.20)	5.51 (1.58–19.2)	17.4 (5.35–56.5)	<0.001
Adjusted HR (95% CI)[b]		Reference	1.48 (0.33–6.66)	2.37 (0.66–8.44)	5.34 (1.58–18.1)	<0.001
Adjusted HR (95% CI)[c]		Reference	1.15 (0.25–5.25)	2.27 (0.64–8.08)	3.48 (1.00–12.1)	0.008
No. cases (detailed)[d]						
Death	16	1	2	2	11	—
Heart failure	51	2	3	12	34	—
Hospitalization	150	26	27	39	58	—
Arrhythmia	109	18	17	33	41	—
Thromboembolic event	24	2	6	8	8	—
Cardiac intervention	112	23	20	33	36	—

Abbreviations: CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RDW, red blood cell distribution width.
[a] Calculated by assigning the median level in each quartile to participants and evaluating this variable continuously.
[b] Adjusted for age (years), sex, congenital diagnosis (aortic stenosis, aortic coarctation or arterial switch operation (0) versus tetralogy of Fallot, Rastelli, systemic RV or univentricular heart [1]), cardiac medication use (yes/no), NYHA class II-III, sinus rhythm (yes/no), systemic ventricular function (0–3).
[c] Additionally adjusted for C-reactive protein and NT-proBNP (both $\log_2$-transformed).
[d] All components of the primary endpoint are separately displayed for exploratory purposes (in which patients were not censored at the time of another endpoint than the endpoint of interest). No comparisons are made between subgroups, in order to avoid multiplicity of comparisons.

endpoint-free. This difference was even more pronounced in patients with the secondary endpoint (Supplemental File 3). In Supplemental Files 4 and 5, the individual measurements are displayed for each patient separately. Our data did not provide evidence for a steady increase in RDW prior to the occurrence of adverse events. The largest part of variation between the RDW measurements was attributable to between-subject variation (76%) instead of within-subject variation (24%).

4. Discussion

In this study, we have prospectively followed a large cohort of ACHD patients during 4.3 years with annual repeated RDW measurements. RDW was higher at study inclusion and throughout the entire follow-up period in patients with a cardiovascular event, especially in patients who died or developed heart failure. Increased RDW at inclusion was significantly associated with cardiovascular events during follow-up, independently of NT-proBNP and other prognostic markers. Adding RDW to a prognostic model including established clinical risk factors and NT-proBNP yielded a modest improvement.

4.1. Previous reports

To our knowledge, this is the first large and prospective study that investigated the prognostic value of RDW in patients with ACHD. The findings of this study are in line with previous studies that have been

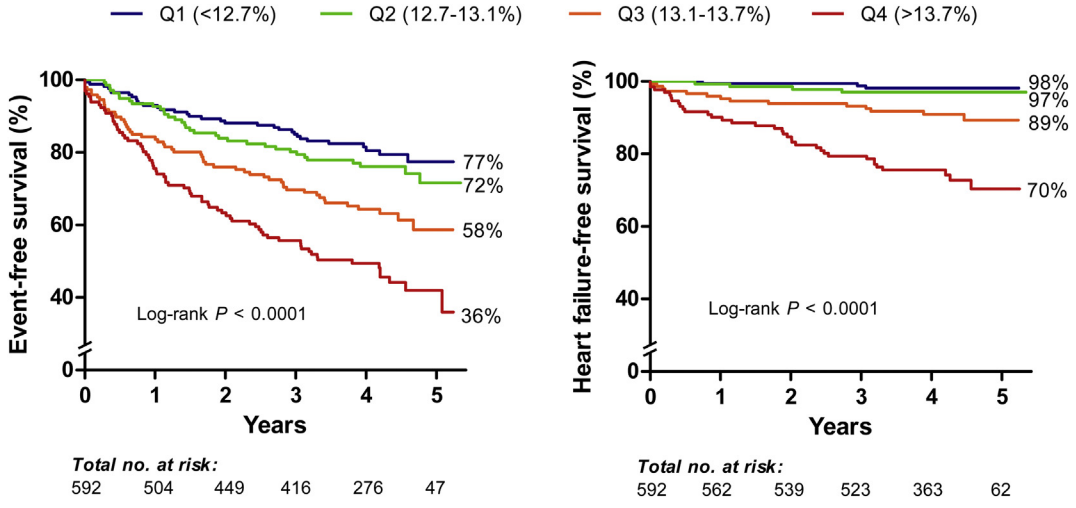

Fig. 1. Kaplan-Meier curves stratified per baseline RDW quartile for the primary and secondary endpoint. Legend: Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

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

Table 3
Associations between baseline hemoglobin, hematocrit, mean cell volume, and red cell distribution and the primary and secondary endpoint, analyzed continuously.

	Crude HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value	Adjusted HR[b] (95% CI)	*P*-value
Cardiovascular event						
Hb, g/L	1.00 (0.99–1.01)	0.572	—	—	—	—
Ht, L/L	2.15 (0.06–79.3)	0.678	—	—	—	—
MCV, fL	1.01 (0.98–1.04)	0.551	—	—	—	—
RDW, %	1.47 (1.34–1.62)	<0.001	1.26 (1.13–1.41)	<0.001	1.20 (1.06–1.35)	0.003
Death or heart failure						
Hb, g/L	0.98 (0.96–1.00)	0.024	0.98 (0.96–1.00)	0.020	0.98 (0.97–1.00)	0.011
Ht, L/L	0.10 (0.00–13.0)	0.209	—	—	—	—
MCV, fL	0.99 (0.94–1.05)	0.731	—	—	—	—
RDW, %	1.81 (1.59–2.06)	<0.001	1.45 (1.23–1.70)	<0.001	1.38 (1.15–1.65)	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age (years), sex, congenital diagnosis (aortic stenosis, aortic coarctation or arterial switch operatio n (0) versus tetralogy of Fallot, Rastelli, systemic RV or univentricular heart [1]), cardiac medication use (yes/no), NYHA class II-III, sinus rhythm (yes/no), systemic ventricular function (0–3).
[b] Additionally adjusted for C-reactive protein and NT-proBNP (both log_2-transformed).

performed in patients with acquired cardiac diseases, such as heart failure and coronary heart disease [2,8–13]. More specific, in a retrospective cohort study of Miyamoto et al. in 144 patients with ACHD who were hospitalized [25], increased RDW was closely related to the risk of cardiovascular death. Comparable results were found in a retrospective cohort of 109 adult patients with Eisenmenger syndrome [26]. Furthermore, RDW was found to be an indicator of iron deficiency in adult Fontan patients and correlated with lower exercise capacity [27]. The remainder of studies that have been performed in congenital heart disease have only included pediatric patients. In a small cross-sectional study of pediatric patients with a Fontan circulation, increased RDW was related to a higher central venous pressure and a lower mixed venous oxygen saturation [28]. In addition, preoperative RDW has been reported to positively correlate with the length of postoperative stay in children undergoing surgery for congenital heart disease [29,30].

4.2. Pathophysiological mechanisms

RDW likely reflects a broad range of pathophysiological processes, that could explain the association between RDW and cardiovascular events in patients with ACHD. First of all, RDW has been directly related to markers of impaired iron mobilization, decreased erythropoietin production, and nutritional deficiencies such as iron, folate, or vitamin B12 [2,3,31]. This may subsequently cause a decreased hemoglobin level, which is associated with a worse prognosis in chronic heart failure patients [32,33]. Nevertheless, data from previous studies and also from our cohort show that RDW provides prognostic information independent of hemoglobin level [10]. Moreover, only 5% of patients had anemia in our study.

Young red blood cells are relatively large and variable in size, and the erythrocytes shrink and become more equally sized during the natural aging process. Oxidative stress and inflammation are both known to decrease red blood cell survival [4,5]. The decreased lifespan of the erythrocytes will lead to relatively large amounts of both large and small red cells, which is reflected by an increased RDW [31]. In addition, RDW has been related to endothelial function as assessed with flow-mediated dilatation (as a measure of underlying metabolic derangements), and a high RDW is more frequently present in patients with kidney failure [34]. Although in our study the average C-reactive protein, total cholesterol, low density lipoprotein and estimated glomerular filtration were within the normal range, RDW seemed to be associated with these measures of inflammation, dyslipidemia and kidney function (Table 1).

The heterogeneity of red blood cell size therefore could be an epiphenomenon that reflects several miscellaneous mechanisms, which are related to an individual's prognosis. Previous studies have shown that risk prediction improves when multiple biomarkers are used together, that reflect distinct pathophysiological mechanisms [21,35]. RDW may combine these different mechanisms in one biomarker, and the red blood cell has therefore been previously proposed as an overall 'barometer' of cardiovascular health [2].

4.3. Clinical implications

The RDW is directly available as part of the automated blood count, which is a routine component of standard blood testing. The measurement is easy, inexpensive, rapid, does not require specific skills or instrumentation, and is readily available in virtually all clinical laboratories worldwide. In light of the accumulating evidence that emphasizes the prognostic value of RDW, the clinical role of RDW may be extended beyond the boundaries of the differential diagnosis of anemia. RDW could be a new tool to enhance the prognostication of ACHD patients, together with other functional, echocardiographic and biochemical markers, and can be easily implemented in routine clinical care. Accurate identification of high-risk patients will enable more intensive follow-up with hopefully prevention of events in the future, and the identification of low-risk patients will lead to reassurance, less intensive follow-up and cost savings.

4.4. Study limitations

Changes in RDW during a hospital admission for acute decompensated heart failure have been previously associated with all-cause mortality or readmission for heart failure [15]. In this study with clinically stable ACHD patients, we did not observe an increase in RDW prior to the occurrence of adverse events. However, RDW measurements were performed only once per year in this study. Therefore, it could be hypothesized that repeated measurements should be performed more frequently in order to find an association between recent changes in RDW and an adverse event.

Imputation of the mean was used to account for the 1% missing NT-proBNP values. Although in general imputation of the mean could be considered as a limitation, it is considered acceptable for covariates with a very low percentage of missing data.

In this cohort, patients with an isolated repaired atrial or ventricular septal defect were not included, due to the expected low number of events in these patients. This should be taken into account when extrapolating these data to other cohorts of patients with ACHD.

5. Conclusions

The RDW is significantly associated with cardiovascular events in patients with ACHD, independently of NT-proBNP and other prognostic markers. This readily available biomarker, that can be reliably measured worldwide at a low cost, may therefore be a valuable additional tool in the risk stratification of patients with ACHD.

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

Acknowledgement of grant support

This study was supported by a grant from the Dutch Heart Foundation, The Hague, The Netherlands (grant number 2015T029).

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.02.118.

References

[1] G.L. Salvagno, F. Sanchis-Gomar, A. Picanza, G. Lippi, Red blood cell distribution width: a simple parameter with multiple clinical applications, Crit. Rev. Clin. Lab. Sci. 52 (2015) 86–105.
[2] L.A. Allen, G.M. Felker, M.R. Mehra, et al., Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure, J. Card. Fail. 16 (2010) 230–238.
[3] Z. Forhecz, T. Gombos, G. Borgulya, Z. Pozsonyi, Z. Prohaszka, L. Janoskuti, Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state, Am. Heart J. 158 (2009) 659–666.
[4] G. Weiss, L.T. Goodnough, Anemia of chronic disease, N. Engl. J. Med. 352 (2005) 1011–1023.
[5] J.S. Friedman, M.F. Lopez, M.D. Fleming, et al., SOD2-deficiency anemia: protein oxidation and altered protein expression reveal targets of damage, stress response, and antioxidant responsiveness, Blood 104 (2004) 2565–2573.
[6] T.S. Perlstein, J. Weuve, M.A. Pfeffer, J.A. Beckman, Red blood cell distribution width and mortality risk in a community-based prospective cohort, Arch. Intern. Med. 169 (2009) 588–594.
[7] K.V. Patel, L. Ferrucci, W.B. Ershler, D.L. Longo, J.M. Guralnik, Red blood cell distribution width and the risk of death in middle-aged and older adults, Arch. Intern. Med. 169 (2009) 515–523.
[8] G.M. Felker, L.A. Allen, S.J. Pocock, et al., Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM program and the Duke databank, J. Am. Coll. Cardiol. 50 (2007) 40–47.
[9] D.A. Pascual-Figal, J.C. Bonaque, B. Redondo, et al., Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients, Eur. J. Heart Fail. 11 (2009) 840–846.
[10] R.R. van Kimmenade, A.A. Mohammed, S. Uthamalingam, P. van der Meer, G.M. Felker, J.L. Januzzi Jr., Red blood cell distribution width and 1-year mortality in acute heart failure, Eur. J. Heart Fail. 12 (2010) 129–136.
[11] G. Turcato, E. Zorzi, D. Prati, et al., Early in-hospital variation of red blood cell distribution width predicts mortality in patients with acute heart failure, Int. J. Cardiol. 243 (2017) 306–310.
[12] N. Shah, M. Pahuja, S. Pant, et al., Red cell distribution width and risk of cardiovascular mortality: Insights from National Health and nutrition examination survey (NHANES)-III, Int. J. Cardiol. 232 (2017) 105–110.
[13] M. Tonelli, F. Sacks, M. Arnold, et al., Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease, Circulation 117 (2008) 163–168.
[14] C.J. Rhodes, J. Wharton, L.S. Howard, J.S. Gibbs, M.R. Wilkins, Red cell distribution width outperforms other potential circulating biomarkers in predicting survival in idiopathic pulmonary arterial hypertension, Heart 97 (2011) 1054–1060.
[15] B.F. Makhoul, A. Khourieh, M. Kaplan, F. Bahouth, D. Aronson, Z.S. Azzam, Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure, Int. J. Cardiol. 167 (2013) 1412–1416.
[16] J.D. Bessman, P.R. Gilmer Jr., F.H. Gardner, Improved classification of anemias by MCV and RDW, Am. J. Clin. Pathol. 80 (1983) 322–326.
[17] A. Karnad, T.R. Poskitt, The automated complete blood cell count. Use of the red blood cell volume distribution width and mean platelet volume in evaluating anemia and thrombocytopenia, Arch. Intern. Med. 145 (1985) 1270–1272.
[18] C.A. Warnes, R. Liberthson, G.K. Danielson, et al., Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (5) (2001) 1170.
[19] H. Baumgartner, P. Bonhoeffer, N.M. De Groot, et al., ESC guidelines for the management of grown-up congenital heart disease (new version 2010), Eur. Heart J. 31 (2010) 2915–2957.
[20] J.A. Eindhoven, A.E. van den Bosch, T.P. Ruys, et al., N-terminal pro-B-type natriuretic peptide and its relationship with cardiac function in adults with congenital heart disease, J. Am. Coll. Cardiol. 62 (2013) 1203–1212.
[21] V.J. Baggen, A.E. van den Bosch, J.A. Eindhoven, et al., Prognostic value of N-terminal pro-B-type natriuretic peptide, troponin-T, and growth-differentiation factor 15 in adult congenital heart disease, Circulation 135 (2017) 264–279.
[22] M.S. Pepe, K.F. Kerr, G. Longton, Z. Wang, Testing for improvement in prediction model performance, Stat. Med. 32 (2013) 1467–1482.
[23] D. Rizopoulos, P. Ghosh, A Bayesian semiparametric multivariate joint model for multiple longitudinal outcomes and a time-to-event, Stat. Med. 30 (2011) 1366–1380.
[24] H. Uno, T. Cai, M.J. Pencina, R.B. D'Agostino, L.J. Wei, On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data, Stat. Med. 30 (2011) 1105–1117.
[25] K. Miyamoto, K. Inai, D. Takeuchi, T. Shinohara, T. Nakanishi, Relationships among red cell distribution width, anemia, and interleukin-6 in adult congenital heart disease, Circ. J. 79 (2015) 1100–1106.
[26] T. Yang, Y.J. Sun, C.M. Xiong, et al., Red blood cell distribution width predicts survival in patients with Eisenmenger syndrome, Clin. Chem. Lab. Med. 52 (2014) 743–750.
[27] L. Tomkiewicz-Pajak, W. Plazak, J. Kolcz, et al., Iron deficiency and hematological changes in adult patients after Fontan operation, J. Cardiol. 64 (2014) 384–389.
[28] T. Kojima, J. Yasuhara, T. Kumamoto, et al., Usefulness of the red blood cell distribution width to predict heart failure in patients with a Fontan circulation, Am. J. Cardiol. 116 (2015) 965–968.
[29] M.M. Massin, Relation between red cell distribution width and clinical outcome after surgery for congenital heart disease in children, Pediatr. Cardiol. 33 (2012) 1021–1025.
[30] S. Kumar, A. Sudhakar, M. Mohan, et al., Elevated red cell distribution width is associated with delayed postoperative recovery after correction of tetralogy of Fallot, Ann. Pediatr. Cardiol. 6 (2013) 121–125.
[31] T.C. Evans, D. Jehle, The red blood cell distribution width, J. Emerg. Med. 9 (Suppl. 1) (1991) 71–74.
[32] C. Opasich, M. Cazzola, L. Scelsi, et al., Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure, Eur. Heart J. 26 (2005) 2232–2237.
[33] J.N. Nanas, C. Matsouka, D. Karageorgopoulos, et al., Etiology of anemia in patients with advanced heart failure, J. Am. Coll. Cardiol. 48 (2006) 2485–2489.
[34] Y. Solak, M.I. Yilmaz, M. Saglam, et al., Red cell distribution width is independently related to endothelial dysfunction in patients with chronic kidney disease, Am J Med Sci 347 (2014) 118–124.
[35] J. Lassus, E. Gayat, C. Mueller, et al., Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: the multinational observational cohort on acute heart failure (MOCA) study, Int. J. Cardiol. 168 (2013) 2186–2194.

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