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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Raised red cell distribution width as a prognostic marker in aortic valve replacement surgery

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Abstract

Background and aim: Several studies have reported that elevated red cell distribution width (RDW) is associated with poor outcomes in patients with coronary artery disease, chronic heart failure and aortic stenosis following transcatheter aortic valve replacement. Their prognostic utility in patients undergoing aortic valve replacement (AVR) surgery is unknown.

Methods: We prospectively evaluated the prognostic value of RDW in a group of 191 consecutive patients with severe symptomatic aortic stenosis undergoing AVR. The pre-defined primary endpoint at the 30-day follow-up was composed of: all cause mortality, perioperative myocardial infarction, perioperative renal failure, prolonged mechanical ventilation, stroke, heart failure, successfully resuscitated cardiac arrest, the occurrence of multiple-organ failure, and the need for additional surgery for any reason. The secondary endpoint was total mortality.

Results: The composite endpoint occurred in 54 patients. In univariate analysis RDW ($p < 0.0001$), haemoglobin level ($p = 0.005$), haematocrit ($p = 0.01$), red blood cell count (RBC; $p = 0.002$), glomerular filtration rate ($p = 0.003$), New York Heart Association classification ($p = 0.02$), atrial fibrillation ($p = 0.0044$), and pulmonary blood pressure ($p = 0.004$) were associated with the occurrence of the composite endpoint. RDW ($p = 0.0005$), haemoglobin level ($p = 0.004$), haematocrit ($p = 0.004$), RBC ($p = 0.0009$) and mean corpuscular volume ($p = 0.01$) were associated with an increased risk of death. In multivariate analysis, RDW (OR 3.274; 95% CI 1.285–8.344; $p = 0.0003$) and RBC (OR 0.373; 95% CI 0.176–0.787; $p = 0.0097$) remained independent predictors of the composite endpoint. Receiver operating characteristic analysis determined a cut-off value of RDW for the prediction of the occurrence of the combined endpoint at 14.1%.

Conclusions: Elevated RDW is associated with a worse outcome following AVR, independent of RBC.

Key words: aortic stenosis, valve disease surgery, inflammatory markers, risk assessment, red cell distribution width

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INTRODUCTION

Red cell distribution width (RDW) is a parameter that reflects the variability of the size of red blood cells. It is calculated automatically or manually by dividing the standard deviation of red blood cell volume and the volume of red blood cells expressed as a percentage. RDW = (standard deviation of mean corpuscular volume [MCV] ÷ mean MCV) × 100. Until now RDW has been used mainly as an auxiliary marker in haematology indicating the increased destruction or impaired production of red blood cells. Several studies have reported that elevated RDW levels are associated with poor outcomes in patients with such cardiovascular diseases as coronary artery disease, idiopathic pulmonary hypertension, chronic heart failure (HF), and severe aortic stenosis after transcatheter aortic valve implantation [1–5]. Its prognostic utility in patients undergoing aortic valve replacement surgery is unknown. Therefore, we attempted to check the prognostic value of RDW in this group of patients.

METHODS

A prospective study was conducted on a group of 191 consecutive patients with severe symptomatic aortic stenosis (a valve area below 1 cm^2 and a mean pressure gradient ≥ 40 mm Hg), who were undergoing elective aortic valve replacement surgery

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at the Institute of Cardiology, Warsaw, Poland. Exclusion criteria were: a lack of consent to participate in the study and age under 18 years. Patients with active neoplastic diseases, autoimmune diseases, and chronic inflammatory bowel diseases were excluded from the analyses. A preoperative complete blood count (a blood sample taken a day before surgery), data on risk factors, the course of operations, and the postoperative period were assessed. Full blood counts were measured from K_2EDTA samples using a Sysmex K-4500 electronic counter.

We also analysed the occurrence of the pre-defined primary composite endpoint in a 30-day follow-up, which consisted of death from all causes and such complications as: perioperative myocardial infarction (defined as the development of new Q waves in two or more leads on an electrocardiogram or alterations of myocardial contractility that did not previously exist in echocardiography), perioperative renal failure (requiring renal replacement therapy), prolonged mechanical ventilation (either mechanical ventilatory support lasting longer than 24 h or the need for reintubation), stroke (evidence of a new neurological deficit or transient ischaemic attack, confirmed by an imaging test), HF (defined as the need for a supply of catecholamines more than 48 h after leaving the cardiopulmonary bypass or the need to resupply), successfully resuscitated cardiac arrest, the occurrence of multiple-organ failure (dysfunction of two or more organs — based on laboratory parameters and/or the need to use organ replacement therapy), and the need for additional surgery for any reason. The length of total hospitalisation and the length of the postoperative stay in the Intensive Care Unit were also recorded. The secondary endpoint was total mortality. The follow-up of discharged patients was conducted through telephone interviews and clinic visits.

The protocol was approved by the Institutional Ethics Committee.

Statistical analysis

Statistical analysis was performed using SPSS software. Univariate analysis followed by multivariate regression analysis was performed. Data are presented as medians with ranges if continuous, or as frequencies if categorical. Results were considered significant when p was less than 0.05. To assess the predictive ability of the RDW, receiver operating characteristic (ROC) curves analysis was used.

RESULTS

One hundred and ninety-one patients after aortic valve replacement surgery with or without other concomitant procedures were examined. In 124 patients a biological aortic valve prosthesis was implanted, and in 67 a mechanical valve. All procedures were performed through a midline sternotomy incision under general anaesthesia in mild systemic hypothermia (temperature 32–34°C).

Table 1 shows the preoperative characteristics of the patients studied. Ten (5.2%) patients had significantly impaired left ventricular systolic function (ejection fraction < 35%) (Table 1).

Table 1. Baseline characteristics of the study population (n = 191)

Preoperative characteristics of patients	Values
Age [years]*	66.2 ± 11.1
Male: men	111 (58.1%)
Previous myocardial infarction	18 (9.4%)
Coronary artery disease	81 (42.4%)
Stroke in history	5 (5.4%)
Atrial fibrillation	38 (19.9%)
Peripheral atherosclerosis	19 (9.9%)
Insulin dependent DM	7 (3.7%)
Hypertension	137 (77.7%)
Current smoker	64 (33.5%)
Hyperlipidaemia	84 (44%)
Body mass index [kg/m^2]*	27.9 ± 4.2
Chronic obstructive airways disease	15 (7.8%)
Chronic kidney disease (GFR < 60)	50 (26.2%)
LVEF [%]*	59.7 ± 11.6
Pulmonary blood pressure [mm Hg]*	39.4 ± 14.1
NYHA classes*	2.4 ± 0.5
Haemoglobin [g/dL]*	13.5 ± 1.4
Haematocrit*	39.6 ± 3.7
Red blood cell count [mln/μL]*	4.4 ± 0.5
Platelets [1000/μL]*	187.7 ± 49.8
RDW [%]*	13.9 ± 0.7
Mean corpuscular volume [fL]*	90.1 ± 7.3
Creatinine [mmol/L]*	86.6 ± 22.3
Bilirubin [μmol/L]*	12.1 ± 9.5
Concomitant CABG	48 (25%)
Concomitant aortic surgery	24 (12.5%)
EuroSCORE II*	2.8 ± 2.1

Values are expressed as mean ± standard deviation* or number (%) of patients; CABG — coronary artery bypass grafting; DM — diabetes mellitus; GFR — glomerular filtration rate, LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; RDW — red blood cell distribution width

In the postoperative period, in the 30-day follow-up, death occurred in 10 patients (the first patient died suddenly — cause of death unknown, the second patient died because of early infective endocarditis, seven patients died as a result of gradually increasing multi-organ failure and the tenth patient died due to post-operative bleeding).

We observed the occurrence of the composite endpoint in 54 patients (perioperative renal failure in six patients, prolonged mechanical ventilation for 21 patients, stroke in three patients and HF in 45 patients). Seven patients were successfully resuscitated after cardiac arrest, and the occur-

Table 2. Analysis of predictive factors for the occurrence of death

Variable	Univariable			Multivariable		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
RDW	2.821	1.574–5.056	0.0005	3.702	1.904–7.196	0.0001
Haemoglobin	0.505	0.315–0.810	0.004			
Haematocrit	0.786	0.668–0.926	0.004			
RBC	0.085	0.020–0.362	0.0009			
MCV	1.219	1.042–1.426	0.01			

CI — confidence interval; MCV — mean corpuscular volume; RBC — red blood cell count; RDW — red blood cell distribution width

Table 3. Analysis of composite endpoint for the occurrence of predictive factors

Variable	Univariable			Multivariable		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
RDW	2.540	1.638–3.939	< 0.0001	3.274	1.285–8.344	0.0003
Haemoglobin	0.711	0.561–0.902	0.005			
Haematocrit	0.895	0.822–0.975	0.01			
RBC	0.330	0.162–0.672	0.002	0.373	0.176–0.787	0.0097
Glomerular filtration rate	0.970	0.951–0.990	0.003			
NYHA classes	2.077	1.117–3.861	0.02			
Atrial fibrillation	2.925	1.398–6.120	0.004			
Pulmonary blood pressure	1.052	1.016–1.089	0.004			

CI — confidence interval; NYHA — New York Heart Association; RBC — red blood cell count; RDW — red blood cell distribution width

rence of multi-organ failure was observed in 16 patients. Rethoracotomy was performed in 20 patients, myocardial infarction occurred in 11 patients. In univariate analysis RDW ($p < 0.0001$), haemoglobin level ($p = 0.005$), haematocrit ($p = 0.01$), red blood cell count (RBC; $p = 0.002$), glomerular filtration rate ($p = 0.003$), New York Heart Association classification ($p = 0.02$), atrial fibrillation ($p = 0.0044$), and pulmonary blood pressure ($p = 0.004$) were associated with the occurrence of the composite endpoint at 30-day follow-up. RDW ($p = 0.0005$), haemoglobin level ($p = 0.004$), haematocrit ($p = 0.004$), RBC ($p = 0.0009$), and mean corpuscular volume ($p = 0.01$) were associated with an increased risk of death. In multivariate analysis, RDW (OR 3.274; 95% CI 1.285–8.344; $p = 0.0003$) and RBC (OR 0.373; 95% CI 0.176–0.787; $p = 0.0097$) remained independent predictors of the composite endpoint. Tables 2 and 3 show the analysis of the predictors of mortality and the composite endpoint.

The real mortality was 5.2 vs. 2.8 expected mortality calculated using EuroSCORE II.

Receiver operating characteristic analysis determined the cut-off value of RDW for the prediction of the occurrence of the composite endpoint at 14.1% (area under curve = 0.7, $p = 0.008$). Figure 1 depicts Kaplan-Meier event-free survival curves for composite endpoint according to the cut-off value of RDW.

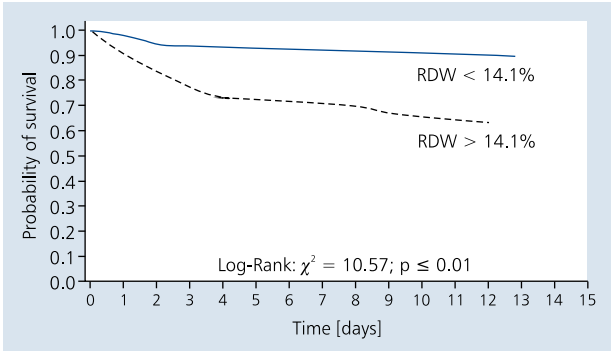

Figure 1. Kaplan–Meier event-free survival curves following aortic valve replacement surgery, for composite endpoint according to the cut-off value of red cell distribution width (RDW)

DISCUSSION

To our knowledge, this is the first report showing the prognostic significance of RDW in predicting complications in patients undergoing aortic valve replacement surgery because of severe stenosis at the 30-day follow-up. RDW is a parameter measured during routine complete blood counts. It carries none of the extra costs and risks associated with the performance of additional diagnostics (which are often invasive). Previous studies have indicated higher values of RDW as an applicable parameter in

the risk assessment and determination of prognosis in patients with coronary artery disease, hypertension, HF, acute coronary syndrome, stroke, and peripheral arterial disease, and in patients undergoing coronary artery bypass surgery [1–3, 6–11].

Moreover, in publications on groups of 250 and 175 patients with severe aortic stenosis those who underwent transcatheter aortic valve implantation showed a significant correlation between elevated RDW and the presence of an increased risk for death and severe complications in a long-term follow-up [4, 5]. In patients undergoing aortic valve surgery Connell et al. [12] demonstrated that an increase in RDW values during the postoperative period was an independent predictor of death in both short- and long-term follow-ups. However, the study has never been published in its entirety, so detailed analysis of the presented data is impossible. The present study demonstrated that RDW is an independent predictor of severe postoperative complications, including death, in a short-term follow-up. In univariate analysis other parameters of the red blood cell system such as RBC, haematocrit, and haemoglobin were associated with the occurrence of the composite endpoint. Worse parameters of the RBC indicate a disturbance in the process of erythropoiesis and consequently increased RDW values. Nonetheless, this parameter was found to be an independent predictor in multivariate analysis.

Preoperative haematocrit is predictive of outcomes after heart surgery [13] as well as in other cardiac conditions, such as HF [14] or acute coronary syndromes [15]. Also, in our series preoperative haematocrit was predictive of outcome, and there were strong correlations between RDW, RBC, and preoperative haematocrit; however, RDW remained an independent prognostic indicator after adjusting for the presence of haematocrit level, RBC, and/or haemoglobin levels. Similar observations were made by other authors in the other conditions, such as HF [16], and also in patients with aortic stenosis undergoing transcatheter aortic valve replacement [5].

According to current knowledge, higher RDW values are associated with inflammatory reaction and oxidative stress because inflammation results in changes in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW [17]. The process of erythropoiesis itself may be disturbed, for which the pro-inflammatory cytokines tumour necrosis factor α, interleukin-1β, and interleukin-6 may be responsible [18–20]. They may contribute to inhibition of bone marrow erythroid progenitor cells, which results in inhibiting erythrocyte maturation and leads to anisocytosis. Further studies have reported a correlation between RDW and such inflammatory markers as high-sensitivity C-reactive protein, erythrocyte sedimentation rate, interleukin-6, and tumour necrosis factor α [21, 22]. Erythropoiesis in oxidative stress results in large immature erythrocytes present in the circulatory system (which increase RDW) [23, 24]. However, owing to their poorer oxygen transportation ability, patients' physiology reserves are lowered. Some authors suggest that RDW is an indicator of a patient's physiologic reserve — the ability of cells to defend against the strong stress of hypoxia [25–27]. The reserve is very important in such stressful situations as surgical intervention. It can explain the higher incidence of complications in patients with elevated RDW.

We still do not know whether elevated RDW is an independent cardiovascular risk factor or a marker of inflammatory reaction or oxidative stress. Nevertheless, the role of RDW as a predictor of mortality in different groups of patients has been widely described. RDW has also been included as a key element of the scales based on complete blood counts assessing the risks of mortality and morbidity [28, 29]. Therefore, on the basis of this work, it appears that RDW may be helpful in selecting a group of patients with a higher risk for postoperative complications requiring additional attention in being qualified for surgery.

Limitations of the study

This study has some potential limitations. It was a single-centred study that included a limited number of participating patients. Further studies are needed to explain the pathomechanisms linking an increased risk for complications in patients with higher values of the RDW.

CONCLUSIONS

Without fully understanding the mechanisms linking a higher risk for complications and a tendency towards increased mortality in patients with anisocytosis, it seems to be too early to name RDW as a simple and widely available prognostic predictor in patients undergoing isolated aortic valve replacement surgery. Further investigation is required, and information about RDW's prognostic value may provide an additional clue for physicians in identifying patients who will not benefit from surgical treatment of aortic stenosis or may be eligible for other types of therapy.

Conflict of interest: *none declared*

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Podwyższona wartość rozpiętości rozkładu objętości erytrocytów jako marker rokowniczy u pacjentów poddawanych operacji wymiany zastawki aortalnej

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Streszczenie

Wstęp: W dotychczasowych badaniach wykazano, że podwyższone wartości rozkładu objętości erytrocytów (RDW) są związane z gorszym rokowaniem u osób z chorobą wieńcową, niewydolnością serca czy ciężką stenozą aortalną leczoną przezcewnikowym wszczepieniem zastawki aortalnej. Znaczenie RDW u pacjentów poddawanych operacji chirurgicznej wymiany zastawki aortalnej jest nieznane.

Cel: Celem niniejszej pracy była ocena wartości prognostycznej RDW u chorych poddawanych operacyjnemu leczeniu ciężkiej stenozy aortalnej.

Metody: Prospektywne badanie przeprowadzono w grupie kolejnych 191 pacjentów z ciężką objawową stenozą aortalną poddawanych operacyjnemu leczeniu wymiany zastawki aortalnej. Na z góry zdefiniowany pierwszorzędowy złożony punkt końcowy w obserwacji 30-dniowej składało się wystąpienie następujących powikłań: zgonu z wszystkich przyczyn, okołozabiegowego zawału serca, okołooperacyjnej niewydolności nerek, przedłużonej wentylacji mechanicznej, udaru ośrodkowego układu nerwowego, skutecznie resuscytowanego zatrzymania akcji serca, niewydolności wielonarządowej i konieczności reoperacji z jakiejkolwiek przyczyny. Drugorzędowym punktem końcowym była śmiertelność.

Wyniki: Pierwszorzędowy złożony punkt końcowy w obserwacji 30-dniowej zaobserwowano u 54 pacjentów. W analizie jednoczynnikowej predyktorami wystąpienia pierwszorzędowego punktu końcowego były: RDW ($p < 0,0001$), hemoglobina ($p = 0,005$), hematokryt ($p = 0,01$), liczba erytrocytów ($p = 0,002$), wskaźnik przesączania kłębuszkowego ($p = 0,003$), stopień niewydolności serca wg klasyfikacji NYHA ($p = 0,02$), migotanie przedsionków ($p = 0,0044$) i ciśnienie w tętnicy płucnej ($p = 0,004$). Wartości RDW ($p = 0,0005$), hemoglobiny ($p = 0,004$), hematokrytu ($p = 0,004$), liczba erytrocytów ($p = 0,0009$) i średnia objętość erytrocytów ($p = 0.01$) wiązały się ze zwiększonym ryzykiem wystąpienia zgonu. Analiza wieloczynnikowa potwierdziła znaczenie RDW (OR 3.274; 95% Cl 1,285–8,344; $p = 0,0003$) jako niezależnego predyktora wystąpienia pierwszorzędowego złożonego punktu końcowego. Przy użyciu statystyki krzywej ROC wyznaczono punkt odcięcia RDW dla wystąpienia złożonego punktu końcowego na poziomie 14,1% (pole pod krzywą 0,07; $p = 0,008$).

Wnioski: Wyższe wartości RDW są związane z gorszym rokowaniem u pacjentów poddawanych operacji wymiany zastawki aortalnej, niezależnie od liczby erytrocytów.

Słowa kluczowe: stenoza aortalna, operacja zastawki, markery stanu zapalnego, ocena ryzyka, rozpiętość rozkładu objętości erytrocytów

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