Hellenic Society of Cardiology (2016) 57, 459–462

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

LETTER TO THE EDITOR

The independent association of two "priceless" parameters: Pulse pressure and red cell distribution width in recently diagnosed hypertensive patients

KEYWORDS
Red cell distribution width;
Aortic stiffness;
Arterial hypertension;
Pulse pressure

Arterial hypertension represents a major risk factor for cardiovascular (CV) disease, leading to subclinical organ involvement, otherwise known as target organ damage (TOD), which is an intermediate stage in the continuum of vascular disease as well as an important determinant of CV risk.[1] Pulse pressure (PP) represents an easy available, reliable, reproducible and inexpensive index of the arterial stiffness and CV risk. Indeed, the Framingham Heart study showed that PP is a strong predictor of coronary events in untreated middle-aged and elderly patients with essential hypertension.[2]

The red cell distribution width (RDW) is a basic parameter of the routine complete blood count and is thus inexpensive, easily counted, widely available, and detected without complex and expensive technologies, although it is overlooked by clinicians as part of the patient evaluation. This blood index expresses the variation in the red blood cell volume in the peripheral circulation, which can be associated with certain disorders. Typically, the RDW spans between 12-15%, and higher RDW values denote greater red blood cell size heterogeneity. Studies demonstrate evidence that the RDW may be a helpful diagnostic and prognostic indicator for acute coronary syndrome, heart failure, peripheral artery disease, metabolic syndrome and obstructive sleep apnea.[3] Higher RDW levels have been found in patients with prehypertension and hypertension compared with normotensive individuals.[4] Because no one has ever explored any relationship between the RDW and PP, two simple and inexpensive indices in arterial hypertension, we investigated any existing relationship between the RDW levels and PP in recently diagnosed and never treated middle-aged patients with mild to moderate essential hypertension.

We studied 135 consecutive hypertensive patients visiting our outpatient clinic with recently diagnosed and never-treated stage I-II essential hypertension according to the 2013 guidelines of the European Society of Hypertension.[1] All patients underwent 24-h ambulatory BP monitoring (ABPM) to confirm the hypertension diagnosis and to exclude white coat hypertension. Participants in our study did not have secondary hypertension or any concomitant disorders and they were not treated with any cardiometabolic medications. The diagnostic work-up has been described in detail in a previous study.[5] RDW was measured as part of the total blood count (blood samples collected in EDTA tubes) obtained from each patient during the diagnostic work-up along with lipid profile, fasting glucose and renal function estimation. Informed consent was obtained from each participant during the initial visit. The study was approved by the ethical committee of our hospital.

The entire population ($n = 135$, mean age 48 ± 11 years, 90 males) was divided into 2 groups according to the office PP quartiles (median value 55 mmHg and 25-75 interquartile range 45-60 mmHg). A PP > 60 mmHg was used as the cut-off level. Group A patients had a similar average 24 h SBP with a significantly lower average 24 h DBP compared to group B patients. The demographic findings, clinical characteristics and laboratory findings of the entire population as well as patients in both groups are listed in Table 1.

The RDW was increased in hypertensive patients with a PP ≥ 60 mmHg ($p = 0.02$). Using Pearson's univariate analysis in the entire population, we found that the RDW was positively related to the office PP ($r = 0.25$, $p = 0.006$, Fig. 1) and probably to the SBP ($r = 0.18$, $p = 0.05$). Further analysis in hypertensives with a PP ≥ 60 mmHg

Peer review under responsibility of Hellenic Society of Cardiology.

http://dx.doi.org/10.1016/j.hjc.2016.11.018

Table 1 Demographic and clinical characteristics, and laboratory findings of the total population as well as the study groups.

	Total population (n = 135)	Hypertensives with PP $\geq$ 60 mmHg (group A, n = 51)	Hypertensives with PP < 60 mmHg (group B, n = 84)	P
Demographic and Clinical Characteristics				
Age (years)	48 ± 11	49 ± 12	47 ± 10	0.22
Male sex (%)	90 (67%)	26 (51%)	64 (76%)	0.005
Weight (kg)	89 ± 18	90 ± 18	88 ± 18	0.53
Body mass index, BMI (kg/m^2)*	29 (27–32)	30 (27–33)	29 (26–32)	0.21
Current smokers (%)	47 (35%)	20 (39%)	27 (32%)	0.64
Total cholesterol (mg/dl)	217 ± 38	217 ± 42	217 ± 36	0.95
Triglycerides (mg/dl)*	120 (88–160)	117 (88–156)	124 (88–171)	0.19
LDL-C (mg/dl)	137 ± 36	137 ± 41	137 ± 33	0.99
HDL-C (mg/dl)	52 ± 16	54 ± 19	50 ± 15	0.21
Creatinine (mg/dl)	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.08
office SBP (mmHg)	148 ± 16	160 ± 13	140 ± 13	<0.001
office DBP (mmHg)	93 ± 11	92 ± 12	93 ± 10	0.69
office PP (mmHg)	56 ± 13	68 ± 9	48 ± 7	<0.001
mean BP (mmHg)*	110 (103–120)	117 (110–121)	108 (101–117)	0.005
24-h SBP (mmHg)	138 ± 11	138 ± 12	137 ± 11	0.78
24-h DBP (mmHg)	86 ± 10	84 ± 11	88 ± 9	0.01
24-h PP (mmHg)	51 ± 8	54 ± 8	49 ± 7	<0.001
24-h Heart rate (bpm)	78 ± 9	78 ± 10	78 ± 8	0.96
RDW (%)	13.5 ± 0.9	13.8 ± 1.0	13.3 ± 0.9	0.006
Target organ damage indices				
PWV (m/sec)	11.6 ± 2.4	11.9 ± 2.6	11.5 ± 2.1	0.44
MAU (mg/24h)*	10 (6–21)	10 (4–18)	11 (7–21)	0.33
cIMT (mm)*	0.9 (0.8–1.0)	0.9 (0.8–0.97)	0.9 (0.8–1.0)	0.35
$CFR_{DIASTOLE}$	2.7 ± 0.8	2.6 ± 0.8	2.8 ± 0.9	0.16
LVMI (g/m^2)	80 ± 18	78 ± 15	81 ± 20	0.37

LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure, RDW = red cell distribution width, PWV = pulse wave velocity, MAU = microalbuminuria levels, cIMT = carotid intima-media thickness, CFR = coronary flow reserve, LVMI = left ventricular mass index. Data are expressed as mean ± SD or as median and 25–75 interquartile range (*), p refers to differences between group A and B hypertensive patients.

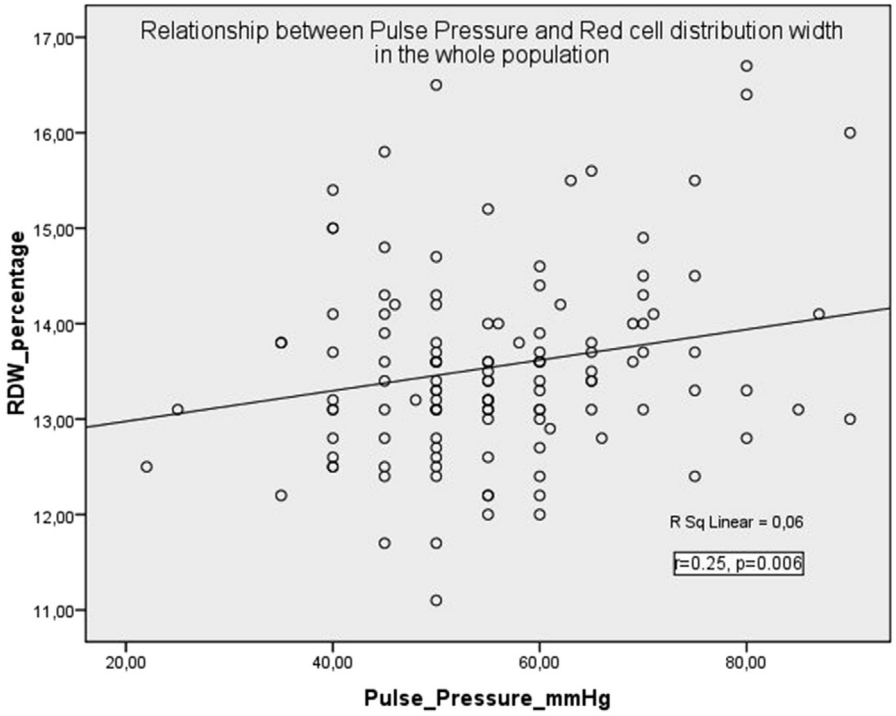

Figure 1 Correlation between pulse pressure (PP) and red cell distribution width (RDW) in the entire population.

Table 2 Pearson's Correlation Coefficients of the relationship between red blood cell distribution width (RDW) with demographic, clinical and laboratory parameters.

Parameter	RDW					
	Total population		Group A		Group B	
	Correlation coefficients	p	Correlation coefficients	p	Correlation coefficients	p
Age	0.12	0.20	0.14	0.33	0.56	0.63
BMI	−0.06	0.53	−0.21	0.15	0.01	0.94
SBP	0.18	0.05	0.26	0.07	−0.07	0.55
DBP	−0.03	0.75	0.04	0.77	−0.07	0.51
Office PP	0.25	0.006	0.33	0.02	0.02	0.90
24-h SBP (mmHg)	−0.08	0.40	−0.10	0.48	−0.08	0.56
24-h DBP (mmHg)	−0.09	0.27	−0.03	0.82	−0.08	0.50
24-h PP (mmHg)	0.02	0.86	−0.09	0.50	−0.01	0.95
PWV	−0.03	0.76	0.09	0.56	−0.15	0.19
MAU	−0.07	0.45	−0.15	0.35	−0.03	0.81
IMT	0.04	0.64	0.12	0.41	0.06	0.61
CFR_D	0.05	0.58	0.13	0.38	0.04	0.71
LVMI	−0.19	0.18	−0.18	0.21	−0.18	0.12

Abbreviations like in Table 1.

showed that the RDW was positively related to the office PP ($r = 0.33$, $p = 0.02$), while a trend was revealed with the SBP ($r = 0.26$, $p = 0.07$). However, no such correlations were revealed in hypertensive patients with a PP < 60 mmHg. In a multivariate stepwise regression analysis of the entire population (age, weight, smoking habit, LDL-C, mean BP and PP were inserted as independent variables), we found an independent relationship between the RDW and office PP ($R^2 = 0.04$, Beta $= 0.20$, $p = 0.02$).

Performing ROC analysis, we calculated the cutoff value of RDW $\geq$ 13.25% as a moderate predictor of an impaired office PP ($\geq$60 mmHg) in the entire population (area under the curve, AUC: 0.61, $p = 0.03$; confidence intervals, CI: 0.51 - 0.71; sensitivity 69% and specificity 51%).

Several studies have tried to explore the significance of "unused" parameters from everyday laboratory findings. Pulse pressure (PP) meets the characteristics of a TOD index; additionally, it seems to supplement the SBP prognostic role in an elderly individual's CV risk. The brachial artery cuff measurement of a large PP in middle-aged and elderly patients becomes a more accurate indicator of the central PP and, subsequently, of a stiffened aorta as well as is an improved predictor of coronary events.[2,6] The latter are more related to the pulsatile stress of large-artery stiffness during systole (as reflected by an increase in PP) than the steady state stress of resistance during diastole (as reflected by a parallel increase in the SBP and DBP).[2]

When the arterial stiffness was estimated by SphygmoCor, the RDW was positively related to the PWV.[7] In our study, using Complior to evaluate the PWV, we did not find a correlation between the PWV and RDW in either the total population or in those patients with an increased PP. We also found that the PWV was only weakly increased in patients with a PP $\geq$ 60 mmHg (median value 11.3 m/sec). We suggest that PP might represent an earlier index of the aortic stiffness in middle-aged and recently diagnosed hypertensive patients compared to the PWV (see Table 2 and Fig. 2).

Several theories have been proposed regarding the underlying pathophysiological mechanisms between the increased RDW, atherosclerosis-related diseases, arterial hypertension, and adverse CV outcomes:

i. The RBC immaturity theory due to bone marrow suppression by a high inflammatory state and increased oxidative stress[8] or due to erythropoiesis

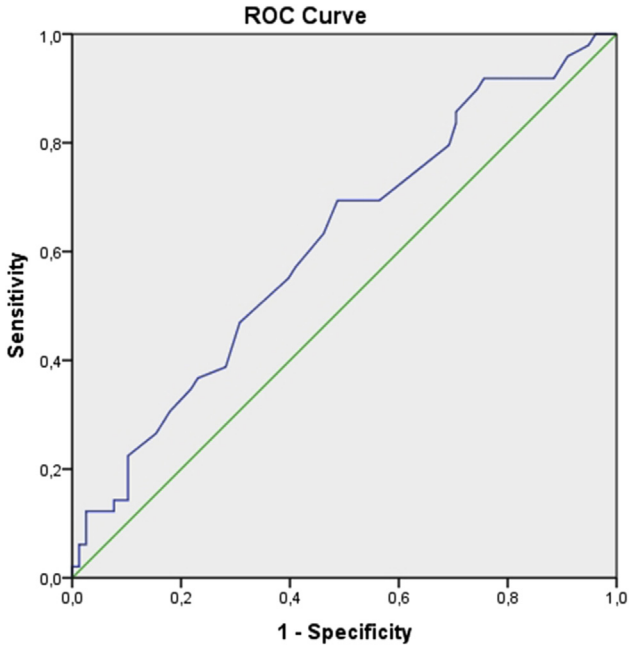

Figure 2 Receiver operating characteristic (ROC) curve analysis of the RDW predicting increased arterial stiffness (expressed as PP $\geq$60 mmHg) in patients with untreated essential hypertension.

stimulation by activated renin-angiotensin-aldosterone and the sympathetic nervous system.[9,10]
ii. The RBC reduced survival theory due to oxidative stress[8] and
iii. The impaired RBC deformity theory due to the increased peripheral resistance in arterial hypertension.[2]

In conclusion, our study provides evidence that the RDW was positively associated with the office PP after adjusting for important confounders, including middle-aged patients, recent diagnosis, and untreated patients with essential hypertension. A physician evaluating the increased RDW in a newly diagnosed hypertensive patient confirms the impaired aortic stiffness that is already suggested by the simple BP measurement and PP estimation.

Declaration of interest

The authors report no conflicts of interest.

References

1. Mancia G, Fagard R, Narkiewicz K, et al. ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159—2219.
2. Franklin SS, Khan SA, Womg ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation*. 1999;100:354—360.
3. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab*. 2014;23:1—20.
4. Tanindi A, Topal FE, Topal F, Celik B. Red cell distribution width in patients with prehypertension and hypertension. *Blood Pres*. 2012;21(3):177—181.
5. Triantafyllidi H, Trivilou P, Ikonomidis I, et al. Is arterial hypertension control enough to improve aortic stiffness in untreated patients with hypertension? A 3-year follow-up study. *Angiology*. 2015;66(8):759—765.
6. Nawrot TS, Staessen JA, Thijs L, et al. Should pulse pressure become part of the Framingham risk score? *J Hum Hypertension*. 2004;18(4):279—286.
7. Fornal M, Wizner B, Cwynar M, et al. Association of red blood cell distribution width, inflammation markers and morphological as well as rheological erythrocyte parameters with target organ damage in hypertension. *Clin Hemorheol Microcirc*. 2014;56(4):325—335.
8. de Gonzalo-Calvo D, de Luxán-Delgado B, Rodríguez-González S, et al. Interleukin 6, soluble tumor necrosis factor receptor I and red blood cell distribution width as biological markers of functional dependence in an elderly population: a translational approach. *Cytokine*. 2012;58(2):193—198.
9. Kato H, Ishida J, Imagawa S, et al. Enhanced erythropoiesis mediated by activation of the renin-angiotensin system via angiotensin II type 1a receptor. *FASEB J*. 2005;19(14):2023—2025.
10. Biaggioni I, Robertson D, Krantz S, Jones M, Haile V. The anemia of primary autonomic failure and its reversal with recombinant erythropoietin. *Ann Intern Med*. 1994;121(3):181—186.

Helen Triantafyllidi*
Leonidas Palaiodimos
Ignatios Ikonomidis
Antonios Schoinas
George Pavlidis
Paraskevi Trivilou
John Lekakis
2nd Department of Cardiology Medical School, University of Athens, ATTIKON Hospital, Athens, Greece

*Corresponding author. Helen Triantafyllidi, MD, 2nd Cardiology Department, Attikon Hospital, Medical School, University of Athens, 83, Agiou Ioannou Theologou, Holargos 155 61, Athens, Greece. Tel: +30 6944268623, fax: +30 210 6522947.
E-mail address: seliani@hotmail.com (H. Triantafyllidi)

27 November 2015
Available online 17 November 2016