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A thousand words about the link between red blood cell distribution width and heart failure

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ABSTRACT

A link between the red blood cell distribution width (RDW) and clinical outcomes in heart failure (HF) was reported for the first time in 2007. Since then, many studies have shown that an increased RDW is an independent and strong predictor of mortality and morbidity in patients with acute, decompensated or chronic HF. The evidence for such a link comes from dozens of prospective and retrospective studies in which clinical data from hundreds or even thousands of patients were examined. Although many processes such as nutritional deficiencies (e.g. iron, folate, vitamin B12), inflammation (interleukin 6, tumour necrosis factor), malnutrition, renal failure or tissue and organ hypoxia have been proposed, no clear explanation exists or is commonly accepted. This mini-review summarises the clinical evidence on the increased RDW as a predictor of adverse clinical outcomes in HF patients, and hypothetical mechanisms that might be responsible for this interesting clinical observation.

Keywords: adverse clinical outcomes; heart failure; mortality, red blood cell distribution width.

Dyspnoea and progressive poor exercise tolerance with early tiredness are typical symptoms of heart failure (HF), which is a consequence of structural remodelling and/or functional impairment of the heart. In HF, cardiac output is reduced due to the compromised contractile ventricular function or generated at the cost of elevated intracardiac pressures owing to impaired diastolic function. The amount of blood pumped by the heart is not sufficient to meet all metabolic body demands for oxygen and nutrients, so all tissues and organs are affected by this disease [1].

Recently, an increased red blood cell distribution width (RDW) has been reported to predict mortality and other major adverse clinical events in HF (**Table 1**) [2, 3, 4, 5, 6]. In 2007, Felker et al. were first who found that an increase in RDW associates with a higher risk for the cardiovascular death or hospitalization in HF patients enrolled to the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program [7]. This observation was confirmed in an independent the Duke Databank — RDW was a strong predictor of mortality [7]. Since then, several other studies showed a similar linkage between elevated RDW and a poor outcome in patients with either acute or chronic HF (**Table 1**).

The RDW is routinely measured by automated haematology analysers as a part of red blood cell count analysis and reported as a component of the complete blood count. Usually, RDW is quantified in two ways. First, as the standard deviation of the size of red blood cells (RDW_{SD}) with the nor-

Table 1. Examples of clinical studies showing an association between RDW and adverse clinical outcomes, including mortality, in patients with heart failure

Study	Study design	Patients	Main findings
the CHARM program [7]	Retrospective	2679 CHF pts	RDW identified as a novel and important predictor of morbidity and mortality in CHF patients
the Duke Databank [7]	Retrospective	2140 CHF pts	Confirmatory analysis of the CHARM cohort — RDW is a predictor of total mortality
Pascual-Figal et al. [22]	Prospective	628 AHF	Increased RDW predicts long-term survival, regardless of haemoglobin concentration and the presence of anaemia
van Kimmenade et al. [23]	Post-hoc analysis	205 AHF	RDW is a one-year mortality predictor after hospital discharge. Prognostic value of RDW is additive to NT-proBNP
STAMINA-HFP Registry [24]	Prospective	1012 CHF	RDW is an independent and strong predictor of both mortality and hospitalisation, even after adjustment for a variety of other clinical and laboratory variables
UNITE-HF Biomarker Registry [24]	Prospective	235	
Makhoula et al. [25]	Prospective	614 AHF pts	RDW independently predicts morbidity and mortality. An increase of RDW in time is also a predictor of mortality.
Muhlestein et al. [26]	Prospective	6414 AHF pts	Elevated RDW and ΔRDW during HF hospitalisation were associated with 30-day mortality
Vizzardi et al. [16]	Prospective	232 CHF pts	RDW predicts better adverse outcomes than echocardiographic parameters
Förhécz et al. [15]	Prospective	195 CHF pts	RDW is a strong, independent predictor of morbidity and mortality
Wasilewski et al. [27]	Retrospective	1734 CHF pts	The highest RDW tertile associates with increased long-term mortality

Abbreviations: AHF — acute heart failure; CHARM — Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CHF — chronic heart failure; STAMINA-HFP — Study of Anemia in a Heart Failure Population; UNITE-HF Biomarker Registry — United Investigators to Evaluate Heart Failure.

mal range between 39 and 47 fL. Second, as the ratio of RDW_{SD} to the mean corpuscular volume of red blood cells, i.e., the coefficient of variation (RDW_{CV}) — this is a unitless parameter with the normal range between 11.5–14.5% [8, 9] (**Figure 1**). The direct interpretation of increased measures of RDW is as follows: the distribution of the red blood cells width is wider than it should be (see the comparison of panels **A** and **B** in **Figure 1**).

Traditionally, an increased RDW is a quantitative measure of anisocytosis, and it is found in various diseases and pathologies of erythrocytes leading to ineffective production or increased destruction of these cells. Some examples of ineffective erythrocyte production are iron, folate or vitamin B12 deficiency, haemoglobinopathies (e.g., sickle cell anaemia, thalassaemia). Increased or accelerated erythrocyte destruction is observed in acute or chronic haemolytic anaemias. For example, in the course of some infections, chronic diseases of other organs (liver or kidneys), toxic or allergic reactions to drugs, venoms, certain foods, autoimmune diseases, hypersplenism or owing to some mechanical narrowing in the blood flow such as severe aortic stenosis or presence of mechanical prosthetic heart valves. Finally, RDW increases after transfusion of red blood cells [8, 10].

In general, an increased RDW suggests that some of the conditions during erythrocyte development were not optimal and mature erythrocytes getting into the circulation had a wide range of different sizes, from small to large. If we consider the usual lifespan of red blood cell of 100–120 days, then an increased RDW means that a substantial part of all circulating red blood cells did not have proper conditions during their development in the bone marrow.

As already mentioned, chronic haemodynamic disarrangements in HF affect all tissues and cells. Co-existence of renal failure, cognitive decline or impairment of the alimentary tract in HF are some examples of how left ventricular dysfunction affects other, remote organs and systems [11, 12, 13]. Thus it is not surprising that the bone marrow function might be modified in HF as well resulting in the altered development of red blood cells.

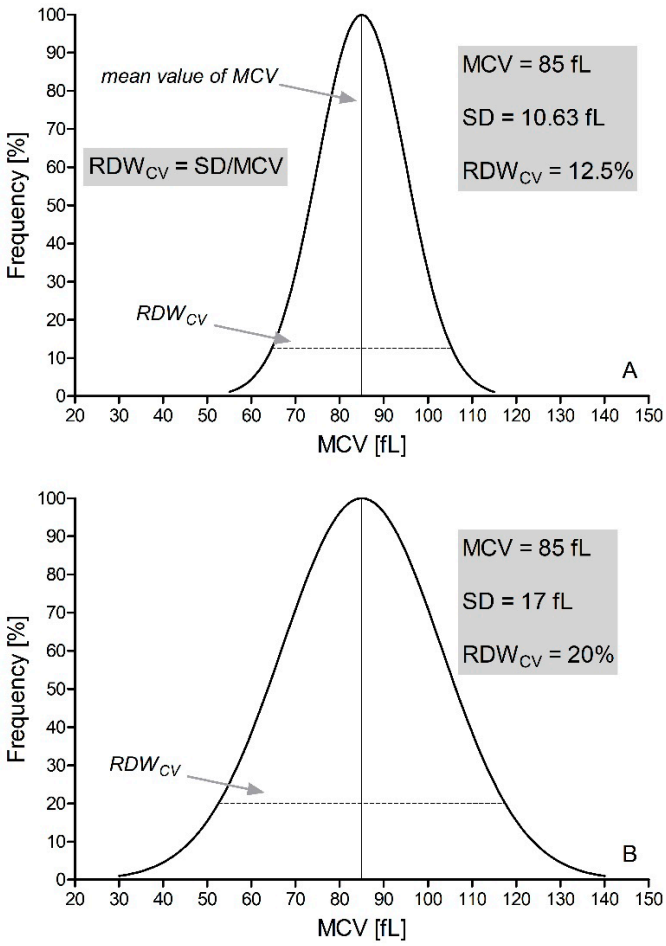

Figure 1. Two examples of theoretical distributions of red blood cell sizes represented by the mean corpuscular volume. Panel A shows normal distribution of the sizes of erythrocytes with RDWcv in the normal range (12.5%). Panel B presents a wider distribution of the sizes of red blood cells with an increased value of RDWcv (20%). Of note, the averaged value of MCV for each distribution of red blood cells is taken as the reference value represented as 100% of the frequency

Potential mechanisms linking HF with RDW

Mechanisms linking RDW and worse clinical outcomes in HF patients are not well understood. Most probably, the anisocytosis observed in HF is a net effect of many different processes and conditions (**Table 2** and **Figure 2**). HF is a complex disease of many causes and consequences. There are nutritional deficiencies due to the dysfunction of the alimentary tract and impaired absorption of various nutrients, including iron, folate and vitamin B12 [14]. Congestion of blood, if right ventricular failure is present, and reduced tissue perfusion, if both left and right ventricles are involved, are typical for HF and may cause dysfunction of kidneys, liver, worse oxygen and carbon dioxide exchange in the lungs. Chronic inflammation is also common in HF patients and may lead to the development of malnutrition and cardiac cachexia. Inflammatory cytokines may alter the function of bone marrow and iron metabolism, including its incorporation to red blood cells. Förhécz et al. have described that markers of inflammation such as cytokines, soluble cytokine receptors, acute phase reactant, were associated with high RDW volume in HF patients [15]. We have observed (**Figure 2**) a significant correlation between the concentration of C-reactive protein and RDW$_{cv}$ in HF patients, both in those who died or survived the three-year follow-up. Reduced production and release of erythropoietin or resistance of bone marrow cells to this hormone observed in HF might contribute as well. [15, 16]. Some cytokines regulating the inflammation may directly inhibit erythropoietin-induced maturation of red blood cells reflected by the elevated worth of RDW [17, 18]. One of

Table 2. Summary of potential mechanisms linking heart failure with increased values of RDW

Mechanism	Explanation
Ineffective Red cell Production [7]	RDW is typically elevated in conditions of ineffective erythropoiesis such as iron deficiency, B12 or folate deficiency. These conditions are not rare in HF patients.
Inflammatory Cytokines, IL-1, IL-6. [28]	Inflammatory cytokines have shown to partially contribute to the pathology of HF. Associations between inflammatory cytokines and RDW have been reported. Chronic inflammation may aggravate HF, and impair iron incorporation to red blood cells in the bone.
Tumour Necrosis Factor Alpha (TNF-a) [24, 29]	TNF-a induces B-adrenergic receptor uncoupling, which then increases reacting oxygen species (ROS) formation and increases Nitric Oxide Synthases (INOS) activity leading to high output NO formation. These mechanisms contribute to HF development and progression. TNF-a interacts with most of the cells in the human body, including bone marrow cells and might influence the development and maturation of red blood cells.
Reticuloendothelial block [24, 31]	Impaired mobilisation and ineffective usage of existing iron stores, even in adequate quantities of iron within the body, is mediated by overexpression of hepcidin, which is synthesised and secreted by the liver and regulates iron metabolism. Hepcidin decreases cell surface expression of ferroportin thus decreasing iron absorption from the intestine and iron release from the reticuloendothelial stores, contributing to an increased RDW and anaemia of chronic disease.
Hypoxia-related aetiologies [32]	Acute or chronic hypoxia stimulates a large increase in serum erythropoietin which then induces the formation of enlarged erythrocytes and increased RDW. Similar RDW increases are seen in multiple acute diseases with the risk of hypoxia such as HF, pneumonia, atelectasis or sepsis.

Abbreviations: HF — heart failure; NO — nitric oxide; TNF — tumor necrosis factor.

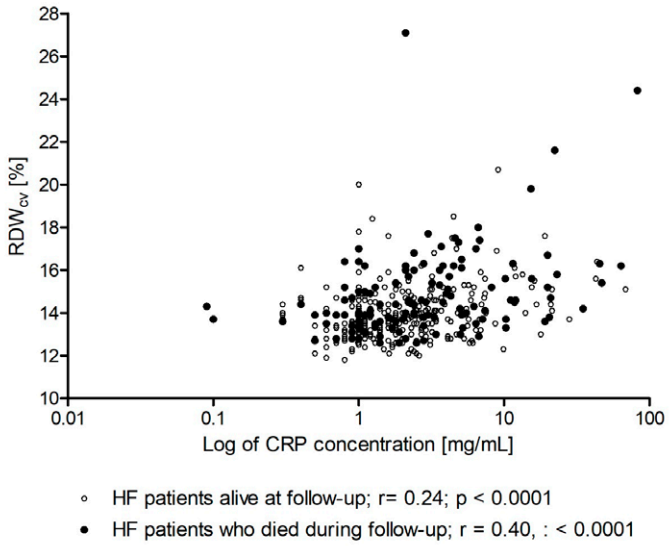

Figure 2. A sample correlation (Pearson) between the concentration of CRP and the value of RDWcv in a group of 419 ambulatory patients with chronic heart failure, reduced ejection fraction < 50% and followed-up up to 3 years. One hundred and four patients died and 295 survived during the 3-year follow-up (unpublished data from the project [33])

the most interesting concepts that might help to link increased RDW with HF is proposed by Yčas et al. who analysed hospital database with hundreds of thousands of patients with different clinical conditions and results of RDW analysis. They have suggested that an increased RDW is a marker of bone marrow hypoxia, which seems to be common in HF patients, particularly those with a more severe form of this disease.

After the initial publication by Felker et al., other studies have shown the association between increased RDW and adverse clinical outcomes in many other non-hematologic disorders like coronary artery disease [3], respiratory diseases [4, 19], stroke [5], critical illness [20], including sepsis [6], or renal failure [21].

Conclusion

There is a solid clinical evidence that an increased RDW is an independent and strong risk

factor for higher mortality and morbidity in HF patients. However, no simple explanation exists for this interesting association between RDW and HF course. Many interesting hypotheses try to explain this association, but so far the mechanisms linking RDW and clinical outcomes in HF patients remain unsolved.

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Conflict of interest statement
The authors declare no conflict of interest.

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