Red Blood Cell Distribution Width as a Link Between Ineffective Erythropoiesis and Chronic Inflammation in Heart Failure

Ryo Inuzuka, MD, PhD; Jun Abe, MD, PhD

Red blood cell distribution width (RDW) is performed as part of a complete blood cell count and quantifies the variability in size of circulating red blood cells, defined as the standard deviation of erythrocyte size divided by the mean corpuscular volume. An increase in RDW reflects the presence of immature red blood cells in the periphery, which is caused by increased red blood cell destruction, pathologic iron homeostasis and ineffective erythropoiesis (Table).

Many recent studies have revealed that increased RDW is a strong predictor of adverse events in patients with heart failure. Although precise mechanisms remain unknown, several potential causes of hampered erythrocyte maturation may be present in heart failure. First, erythropoietin (EPO) secretion is decreased in patients with both heart failure and impaired renal function. Second, heart failure is accompanied by a chronic inflammatory state with increased circulating proinflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-1, and IL-6, all of which inhibit EPO production, blunt EPO response and reduce functional iron availability. In particular, IL-6 induces ferritin expression and stimulates iron retention within macrophages, leading to a decreased iron concentration in the circulation and thus to limited availability of iron for erythroid cells. Moreover, IL-6 stimulates the hepatic expression of hepcidin, which inhibits duodenal iron absorption and blocks iron release from macrophages. RDW may represent an integrative marker of multiple pathologic processes in heart failure.

Patients with adult congenital heart disease (ACHD) are an anatomically heterogeneous population, but have the characteristics of chronic heart failure in common, such as neurohumoral activation in accordance with symptom severity and ventricular dysfunction. This growing population is now recognized as a chronic heart failure syndrome. Similar to acquired heart disease, anemia is a strong predictor of mortality in noncyanotic ACHD. Moreover, in the same study, those with anemia had lower mean corpuscular volume, suggesting a possible role of iron deficiency in the pathogenesis of heart failure in noncyanotic ACHD. In cyanotic patients, secondary erythrocytosis develops as a physiological adaptive response for increasing oxygen delivery to peripheral tissues by increasing oxygen carrying capacity and total blood volume. Iron deficiency is prevalent in cyanotic patients because of the increased iron demand resulting from secondary erythrocytosis. In cyanotic ACHD, iron deficiency anemia is reported to relate to cerebrovascular events. Thus, iron deficiency and ineffective erythropoiesis are likely to be a key issue in ACHD, whereas iron homeostasis, especially in the presence of cyanosis, would differ between congenital and acquired heart disease. Therefore, the clinical significance of RDW, a marker of ineffective erythropoiesis, needs to be elucidated specifically in the ACHD population. In cyanotic ACHD, RDW has been reported to be a marker of iron deficiency anemia. As anemia is an established risk factor for mortality in ACHD, it has been of clinical interest whether RDW carries incremental prognostic information or is just a correlate of anemia.

In this issue of the Journal, Miyamoto et al provide important data showing that RDW relates to cardiovascular mortality in ACHD independently of the presence of anemia. Moreover, they demonstrate a positive correlation between RDW and IL-6, a link between markers of ineffective erythropoiesis and chronic inflammation, respectively. These findings confirm the presence and effect of pathologic iron homeostasis caused by persistent inflammation in ACHD patients, similar to other forms of chronic heart failure syndrome. Owing to the retrospective nature and limited sample size of the current study, the implications of these findings should be interpreted with caution.

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Department of Pediatrics, The University of Tokyo, Tokyo (R.I., J.A.), Japan

Mailing address: Ryo Inuzuka, MD, PhD, Department of Pediatrics, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: inuzukar-tyk@umin.ac.jp


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there are several limitations. Detailed information on iron status was not available. In cyanotic patients, defining “anemia” (ie, iron-restricted erythropoiesis) is difficult without indices of iron status (eg, ferritin, iron, total iron binding capacity and transferrin saturation), but in the present study the hemoglobin level for anemia was based only on percutaneous oxygen saturation. Moreover, because of the limited number of events, potential confounders were not fully adjusted. For instance, the presence of cyanosis is an important confounder, as it is known to affect RDW and mortality.14

Despite these limitations, it is clear from this study that RDW is an inexpensive and useful marker of adverse outcomes in ACHD. Thus, RDW is likely to reflect pathologic processes of heart failure common among acquired and congenital heart disease patients. EPO resistance, inadequate bone marrow response to EPO, leading to an impaired erythropoiesis, is associated with morbidity and mortality in acquired heart disease.16 It has been hypothesized that EPO resistance could explain the association between RDW and adverse outcomes. However, a previous study showed that EPO resistance was not associated with RDW, but that RDW was associated with reduced functional iron availability.1 Further studies are warranted to clarify the pathophysiological mechanisms responsible for the association between RDW and adverse outcomes.

References


