

Editorial

Red Cell Distribution Width Measurement: What Role Does It Have in Heart Failure?

Determinación del ancho de distribución eritrocitaria. Utilidad en la insuficiencia cardiaca

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Over the past decade, there has been a literal explosion of studies examining various prognostic biomarkers in patients with heart failure. Some of these biomarkers—such as the natriuretic peptides—directly reflect pathophysiologic processes in the diagnosis, while the prognostic links for other “heart failure biomarkers” remain less well-defined.

In the article published in *Revista Española de Cardiología*, Bonaque et al. present their data demonstrating the prognostic role of the red cell distribution width (RDW) in 698 subjects suffering from chronic heart failure.¹ In adjusted analyses, RDW predicted mortality, as well as hospitalization in chronic heart failure, and reclassified risk beyond standard variables. The authors also identified a practical RDW cut-point of 15.4% (quite consistent with prior studies of RDW) as the upper reference limit for this curious “biomarker”. Their study confirms the previously established association between RDW and morbidity and/or mortality in subjects suffering from the complete spectrum of cardiovascular diseases.

After the initial publication by Felker et al. in 2007² reporting that RDW was fortuitously found to be a powerful independent predictor of prognosis in heart failure (and importantly, superior to other parameters of anemia including hemoglobin concentrations), RDW became the subject of interest of various clinical investigators working in the field. Across a broad range of cardiovascular diseases, including heart failure, RDW has been found to be a consistent, independent predictor of outcome. The key question at present is whether RDW should be routinely measured for patient management, as Bonaque et al. suggest.

Recently, we proposed 4 conditions which we believe any novel biomarker in heart failure should fulfill in order to become clinically relevant and widely used³; using this context, it is worthwhile and important to evaluate RDW in order to see whether it meets these conditions.

Firstly, we suggested that the “statistical methods by which any novel biomarker is investigated should be thorough, including robust comparisons to other previously established biomarkers,

and the novel marker should be evaluated across a range of patients.” In the present study Bonaque et al. employed rigorous statistical methods, but unfortunately did not examine the prognostic value of RDW relative to natriuretic peptides, the “gold standards” for heart failure prognosis⁴; nonetheless, others have undoubtedly shown additional prognostic value of RDW on top of B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide.^{5,6}

Secondly, we noted that “for a novel biomarker to be useful, its measurement should be performed easily, within a short period of time, and provide acceptable accuracy with defined biological variation and low analytical imprecision.” While widely measured via standard of practice, the imprecision values for RDW are not defined, and the biological variability of the biomarker—crucial to understand if it is to be serially measured—is not known. Thus, although RDW is already an accepted parameter for its hematologic applications, serious limitations exist for its use for heart failure evaluation and management.

These initial two considerations thus considered, it unfortunately gets even more complex: as we further argued, “any novel clinically relevant heart failure biomarker should primarily reflect important (patho)physiological process(es) involved in heart failure and its progression, while the use of a biomarker that originates outside the myocardium is acceptable as long as such a biomarker independently provides information involved in the diagnosis, prognosis, progression, or therapy of heart failure.” A prime example of this latter rule would be use of renal biomarkers for heart failure risk stratification and management: while not strictly related to “heart failure” *per se*, the tight entanglement of the cardiac and renal systems from a pathophysiologic, prognostic, and therapeutic standpoint makes the measurement of such biomarkers (such as estimated glomerular filtration rate) in a heart failure patient quite logical. On the other hand, it remains quite unclear *what* RDW is reflecting in our patients with heart failure.

RDW is not a molecule but a statistical concept: it is a measure of the variation in volume of the red blood cells, originally introduced as an aid in the diagnostic work-up in normocytic anemia. Anemia is common and associated with poor prognosis in heart failure,⁷ often related to either renal disease and/or erythropoietin resistance in such patients,⁸ but we and others have shown the prognostic value of RDW supercedes that of

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anemia presence and severity. Emans et al. have recently shown that RDW was associated with functional iron availability, erythropoietic activity, and interleukin-6 in their anemic heart failure patients with chronic kidney disease,⁹ findings in line with those by Allen et al. who also found an association between an elevated RDW and inflammatory stress as well as with impaired iron mobilization.¹⁰ Accordingly, RDW may simply reflect inflammation as part of the so-called “cardio-renal anemia syndrome.”¹¹ On the other hand, given links between RDW and outcome even in normal subjects^{12,13} this is hard to support.

This stated, our fourth criterion logically follows: “for any novel biomarker to gain clinical relevance, it must provide useful information for caregivers and patients to facilitate more swift and reliable establishment/rejection of a diagnosis, a more accurate estimation of prognosis, or to inform more successful therapeutic strategies.” RDW appears to be prognostically meaningful, but this is an empty finding if such risk cannot be changed; thus, unless and until the mechanistic reasons for the value of RDW are elucidated, a therapeutic imperative associated with its management cannot be derived and tested. This is the necessary next step in RDW-related research in heart failure.

In summary, Bonaque et al. have added another excellent chapter to the intriguing story of RDW in cardiovascular disease. While RDW has repeatedly impressed with its ability to predict adverse outcomes, this is about the only thing clear about it. Thus, it is premature to specifically measure and use it for patient management, as suggested by the authors. That said, the infrastructure for measurement of RDW is present in every lab that can measure hemoglobin concentrations, and its measurement is strikingly cost-effective. Thus, when indeed a mechanistic understanding of an elevated RDW is developed and therapeutic consequences are identified for such a scenario, it is highly possible RDW will become a member of the standard evaluation test panel for our heart failure patients, side by side with renal function assessment and natriuretic peptide measurement.

CONFLICTS OF INTEREST

None declared.

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