# A RELEVÂNCIA DO ÍNDICE DE ANISOCITOSE NA DOENÇA CAROTÍDEA

## *THE ROLE OF THE RED CELL DISTRIBUTION WIDTH IN CAROTID ARTERY DISEASE*

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## RESUMO

**Introdução:** A doença carotídea afeta 3-4% da população geral. A associação entre inflamação sistémica de baixo grau e aterosclerose estimulou o estudo de biomarcadores sanguíneos, nomeadamente o índice de anisocitose (RDW-CV), e a sua importância na fisiopatologia e prognóstico da doença carotídea. O objetivo deste estudo foi elaborar uma revisão da literatura no que diz respeito à relevância do RDW-CV na doença carotídea.

**Métodos:** Foi realizada uma pesquisa na base Medline de forma a identificar publicações focadas na fisiopatologia do RDW-CV e o seu impacto na doença carotídea.

**Resultados:** Um aumento de RDW-CV associou-se a um espessamento íntima-média carotídea (CIMT) em vários estudos. Associou-se à presença de placas de aterosclerose e sua progressão. Um estudo demonstrou uma associação independente entre mortalidade por todas as causas e mortalidade cardiovascular com o aumento do RDW-CV em doentes com estenose carotídea assintomática.

**Conclusão:** O RDW-CV é um marcador de baixo custo, prontamente disponível e fácil de se obter que parece estar associado a aterosclerose carotídea subclínica. Contudo são necessários mais estudos para se determinar a sua importância clínica neste contexto.

### Palavras-chave
Doença arterial carotídea; Determinação de tamanho eritrocitário; Biomarcadores

## *ABSTRACT*

***Introduction:*** *Carotid disease affects 3-4% of the general population. The association between systemic low-grade inflammation and atherosclerosis has led to the study of blood biomarkers, such as red blood cell distribution width - coefficient of variation (RDW-CV), and their role in the pathophysiology and prognosis of carotid artery disease. The aim of this study was to review the literature regarding the relevance of RDW-CV in carotid artery disease.*

***Methods:*** *A Medline search was performed in order to identify publications focused on the physiopathology of RDW-CV and its impact in patients with carotid artery disease*

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***Results:*** *Increased RDW-CV was associated with increased carotid intima-media thickness (CIMT) in several studies. It was associated with plaque presence and progression. One study demonstrated an independent association between all-cause and cardiovascular-related mortality in patients with asymptomatic carotid artery stenosis and increased RDW-CV.*

***Conclusion:*** *RDW-CV is a widely available, easy to measure, and low-cost marker that seems to be associated with subclinical carotid atherosclerosis. However, further studies are needed in order to determine its clinical relevance in this setting.*

### *Keywords*
*Carotid artery disease; Erythrocyte size determination; Biomarkers*

## *INTRODUCTION*

*Carotid disease affects 3-4% of the general population with varying degrees according to age, gender and race[1]. It is a major risk factor for ischemic stroke, with ipsilateral carotid atherosclerosis accounting for 20-30% of these events[2]. Patients with ≥50% carotid artery stenosis have an annual stroke risk of 0.34% and an annual transient ischemic attack (TIA) risk of 1.78%[1]. Despite the improved outcomes in recent years, stroke still poses a high burden of morbidity and mortality, leaving impaired half of those who survive[3]. Sustained low-grade inflammation is linked to the development of atherosclerotic disease in several vascular beds[4]. This pathophysiological mechanism has spiked the interest in the association between blood biomarkers and the development of carotid artery disease and outcomes after revascularization. One of such biomarkers is red blood cell distribution width - coefficient of variation (RDW-CV).*

*RDW-CV is an hematological parameter that reflects heterogeneity of red blood cells (RBC) volume (anisocytosis) and it is defined by the ratio between RBC standard deviation and mean corpuscular volume, multiplied by 100, with values below the reference limit being infrequent and clinically meaningless[5]. Conversely, increased RDW-CV has been related to deregulation of erythrocyte homeostasis, including impaired erythropoiesis and abnormal erythrocyte metabolism and survival. Increased RDW-CV was initially acknowledged as a marker of iron deficiency[6]. However, several additional potential mechanisms have been proposed for the increase of RDW-CV, such as nutritional deficiency (vitamin B12, folic acid), bone marrow depression, or inflammation, which leads to the extension of red blood cell lifespan[7]. Recent studies have pointed out a link between RDW-CV, diabetes mellitus (DM), and inflammation. RDW-CV is also strongly associated with stroke and MI incidence[8]. Furthermore, it seems to be a reliable and independent predictor of mortality in coronary artery disease (CAD) and ischemic stroke[9,10].*

*The association between RDW-CV and carotid artery disease has also been studied. The aim of this study was to review the literature regarding the relevance of RDW-CV in the subpopulation of vascular patients with carotid artery disease.*

## *METHODS*

*A Medline search was performed in order to identify articles focused on these RDW-CV and its pathophysiology and effect on outcomes in carotid artery disease. Keywords used for research included "carotid disease", "red cell distribution width", "hematological parameters," and "carotid endarterectomy". Additional articles of scientific interest for the purpose of this non-systematic review were included by cross-referencing. Primary endpoints were to describe association between RDW-CV and carotid disease progression. Association between RDW-CV and demographic features was also assessed.*

## *RESULTS*

### *Clinical demographics*

*In a study by Wonnerth et al. involving 1065 patients, among patients with asymptomatic carotid stenosis, increased RDW-CV was associated with older age (p=0.001), lower levels of high-density lipoprotein cholesterol (c-HDL) (p=0.007), history of stroke (p=0.049), coronary artery disease (p=0.004) or myocardial infarction (p=0.015) and lower estimated glomerular filtration rate (eGFR) (p<0.001). There were no differences in RDW-CV between genders[11].*

### *Carotid intima-media thickness*

*Söderholm et al. demonstrated in a population based survey of 26879 participants in Malmö that increased RDW-CV was independently associated with increased carotid intima-media thickness (CIMT) in the common carotid artery (p=0.011) but not in the carotid bifurcation[12]. Similarly, an independent association between increased RDW-CV and increased CIMT was demonstrated in three other studies[13-15]. Thus, evidence points to an association between increased RDW-CV and subclinical atherosclerosis.*

***Carotid plaques***

*The Tromsø study was a population based study involving 27158 subjects above 24 years old. Among these, 6727 underwent carotid duplex ultrasound (DUS) examination at baseline, with 4858 undergoing DUS at seven years of follow up. Increased RDW was associated with carotid plaque presence, area at baseline and was independently associated with plaque progression, with and increased of 0.6mm2 in plaque area by each increase of 1% in RDW-CV[16]. In another study, Wen et al. demonstrated in a sample of 156 hypertensive patients that RDW-CV was associated with the presence of carotid plaques[17].*

***Carotid artery stenosis***

*Wonnerth et al. evaluated 1065 patients with asymptomatic carotid artery stenosis in a prospective cohort study for a median of 6.2 years. RDW was found to be significantly associated with all-cause mortality (aHR from 0.89 to 1.94 for the highest vs the lowest quartile) and with cardiovascular mortality (aHR from 1.08 to 2.34 for the highest vs the lowest quartile)(11) No data was found on any association between RDW and carotid-related symptomatic status. It is also unknown if RDW-CV is related to the degree of carotid artery stenosis.*

***Post-operative outcomes of carotid artery revascularization***

*Bojakowski et al. performed a retrospective case-control study involving 115 patients submitted to carotid endarterectomy and followed up to 18 months. Increased baseline RDW-CV was associated with death or restenosis (p=0.0234) and death, restenosis, TIA or any revascularization (p=0.0155) (18). However, no adjustment for confounding was performed and the real significance of these findings is unclear.*

## *DISCUSSION*

*This review highlights the recent interest in the association between a specific biomarker and the development and clinical course of extracranial cerebrovascular disease.*

*The association between RDW-CV and adverse events has been studied in many cardiovascular diseases. In a large prospective study involving 240,477 healthy volunteers, increased baseline RDW-CV was independently associated with incidence of CAD, stroke, atrial fibrillation, peripheral vascular disease and heart failure[19]. In a study by Poludasu et al. increased RDW-CV was independently associated with long-term all-cause mortality in patients undergoing percutaneous coronary intervention[9], regardless of hemoglobin values. Gurbuz et al. demonstrated that increased baseline RDW-CV is an independent predictor of long-term major adverse cardiovascular events after coronary artery bypass grafting[20]. Xanthopoulos et al. concluded that RDW-CV is an independent predictor of death or rehospitalization in patients with heart failure[21].*

*The pathophysiological mechanisms that link RDW-CV to atherosclerosis and cardiovascular events are still largely unclear, although some hypotheses have been proposed. Reduced iron reserves, independently of hemoglobin levels, are associated with increased RDW-CV and could play a role in atherogenesis[22]. Inflammation may be the link between increased RDW-CV and cardiovascular events. Higher RDW-CV values are independently associated with raised inflammatory parameters[23] and it is well established that inflammation is a critical factor in plaque progression and vulnerability. RDW-CV is considered by some to be a marker of inflammation[22].*

*As noted earlier, increased RDW-CV has been associated with increased CIMT in several studies. Thus, one can propose that is linked with the pathogenesis of carotid atherosclerosis. However, many questions remain unanswered. It is yet to be known if increased RDW-CV is associated with different degrees of carotid artery stenosis. It is also unknown if it is associated with plaque vulnerability and risk of ipsilateral carotid related stroke. If an associated is found, it could prove helpful in selecting a subset of asymptomatic patients who would benefit from carotid revascularization. On the other hand, it could help determine who would not live long enough to benefit from any intervention other than the state of the art medical treatment.*

*Although this review has shown some interesting findings, there are a few limitations to be considered. Due to the non-systematic nature of the search method, it is likely that not all the relevant literature was retrieved. There is also the possibility of publication bias, since non-positive results are easily less evident during research. All retrieved studies are observational.*

*The utility of RDW-CV in clinical practice is yet unknown*

*Further studies are needed in order to ascertain the pathophysiological and clinical relevance of this biomarker in carotid artery disease.*

## *CONCLUSION*

*RDW-CV is a widely available, easy to measure, and low-cost marker that seems to be associated with subclinical carotid atherosclerosis. However further studies are needed in order to determine its clinical relevance in this setting.*

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