

Inflammation, Hemodynamics, and Carotid Plaque: A Phenotype in Need of Validation

Inflamación, hemodinamia y placa carotídea: un fenotipo que pide validación

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More than two decades ago, we stopped thinking of atherosclerosis as a simple lipid deposit in the arterial wall and began to understand it as a chronic inflammatory disease. (1) For years, this idea was supported by observational data, until the JUPITER and CANTOS studies were published, showing that reducing inflammation without altering LDL cholesterol decreases cardiovascular events. (2,3) However, in clinical practice, high-sensitivity C-reactive protein (hs-CRP) is still ordered inconsistently, and the other half of the story—the hemodynamics to which the endothelium is exposed—is virtually never measured in the routine evaluation of patients at cardiometabolic risk.

The study by Chong et al., published in this issue of the journal, attempts to bring these two dimensions together. (4) The authors analyzed 243 outpatients with hypertension and diabetes or prediabetes, evaluated at a center in the Buenos Aires metropolitan area, and defined a low-flow, high-resistance hemodynamic-inflammatory phenotype (FIBFAR) based on the combination of hs-CRP ≥ 2.5 mg/L, cardiac index (CI) < 2.5 L/min/m², and systemic vascular resistance (SVR) > 1600 dynes·s·cm⁻⁵, with the latter two measures obtained via impedance cardiography. Twenty-three percent of the cohort met the FIBFAR criteria, and of these, three out of four had carotid plaque. The association was maintained in the multivariate analysis (OR 8.60; 95% CI: 4.39–17.70), with a well-calibrated model and moderate discriminatory power (AUC 0.73).

The study has several merits. The objective is highly clinical: to identify, using a blood sample and a test that takes only a few minutes, patients who likely already have plaque, without resorting to expensive methods or highly specialized centers. Methodologically, the cutoff points were established before analyzing the data; the number of covariates adheres to the

ratio of ten events per variable (5); and the authors are careful to speak of association rather than prediction. Furthermore, we find it significant that the data are from Argentina, involving real outpatient patients, in a field where almost all the data we use come from cohorts in the Northern Hemisphere. The pathophysiological hypothesis is also consistent. Low-grade inflammation impairs endothelial function, reduces nitric oxide availability, and increases vasoconstrictor tone; it is reasonable to assume that patients with both inflammation and high-resistance, low-flow circulation are more susceptible to arterial wall damage. I would like to add a few reflections on the path this phenotype might take to extend beyond the center where it originated.

One has to do with thresholds. The authors' exploratory analysis shows that the optimal cutoff for cardiac index (CI) coincided with the chosen value (2.5 L/min/m²), that the cutoff for hs-CRP was somewhat higher (3.2 mg/L), and that the cutoff for SVR was significantly higher (2235 dynes·s·cm⁻⁵). In treated hypertensive patients, SVR tends to be high in almost all cases, and in fact, the median exceeded 2000 dynes·s·cm⁻⁵, with and without plaque. Testing more stringent thresholds, or using the systemic vascular resistance index so that cardiac output and resistance are expressed in the same way, could refine the hemodynamic component. Regarding hs-CRP, the value of 2.5 mg/L falls between the classic thresholds of the AHA and CDC (6) and the 2 mg/L threshold from JUPITER, making it a reasonable choice.

Another factor is physiological, and I believe it strengthens the authors' hypothesis. In this cohort, low flow coexists with a preserved ejection fraction (median of 63–65%), which points more toward a problem with afterload, ventricular-arterial coupling, or preload than with systolic function. Consistent

REV ARGENT CARDIOL 2026;94:359-360. <https://doi.org/10.7775/rac.v94.i5.21058>

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with this, the pulse pressure was somewhat higher in patients with plaque, and the use of diuretics was more frequent in them, although the differences are small. It is possible that part of what FIBFAR captures is arterial stiffness and vascular aging. (7) If so, FIBFAR would serve as a comprehensive marker of arterial wall status, a concept that could be further explored by incorporating pulse wave velocity in future studies. (8)

It remains to be seen to what extent hemodynamics contributes to inflammation. The two phenotypes with elevated hs-CRP had the highest prevalence of plaque (75% in FIBFAR and 56% in the inflammatory-vasoconstrictor phenotype), and hs-CRP alone achieved an AUC of 0.70. Comparing models with and without hemodynamic components, using likelihood ratio tests or reclassification indices (9) would allow us to quantify the incremental value of impedance. In a validation cohort, it would also be useful to use the adaptive phenotype as a reference, expand the adjustment to include LDL cholesterol, lipid-lowering therapy, and renal function, and acknowledge that, with two-thirds of patients on statins, LDL measured in a cross-sectional study provides little insight into the cumulative exposure that led to plaque formation.

The authors honestly acknowledge the remaining limitations: the lack of assessment of intra- and inter-observer variability in impedance cardiography; the exclusion of patients with a body mass index >35 kg/m² for technical reasons, which leaves out a significant portion of the highest-risk population; and the cross-sectional design, which does not allow to establish the direction of the relationship. This relationship may well be bidirectional, because inflammation promotes plaque formation, but plaque also causes inflammation.

The value of this study lies in proposing a different way of assessing risk—beyond lipid profiles and traditional scores—using tools that are accessible and applicable to our population. The next step is to validate the phenotype in an independent, multicenter cohort, examine how it varies by sex, age, and degree of obesity, and follow these patients over time. I am left with one question that really intrigues me: whether the phenotype changes with interventions that act on both axes—such as statins, colchicine, or GLP-1 re-

ceptor agonists (2, 10, 11)—and whether that change is accompanied by slower plaque progression. The authors have opened a line of research that deserves to be continued, and hopefully we will soon see the next steps in these very pages.

Conflicts of interest

The author declares that she has no conflicts of interest related to the editorial

(See authors conflicts of interest forms on the website).

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