

FIBFAR: Hemodynamic-Inflammatory Phenotype Associated with Subclinical Carotid Atherosclerosis in Patients with Cardiometabolic Risk

FIBFAR: Fenotipo hemodinámico-inflamatorio asociado con aterosclerosis carotídea subclínica en pacientes con riesgo cardiometabólico

PAOLA CHONG VELÁSQUEZ¹, PEDRO FORCADA², MTSAC, NICOLÁS MOSTEIRO³

ABSTRACT

Background: Systemic inflammation and hemodynamic alterations represent complementary pathophysiological mechanisms involved in cardiovascular disease. The identification of integrative phenotypes using noninvasive tools could contribute to better characterization of subclinical atherosclerosis.

Objective: To evaluate the association between the low-flow, high-systemic vascular resistance hemodynamic-inflammatory phenotype (FIBFAR) and the presence of carotid plaque in patients with cardiometabolic risk, defined by the presence of hypertension and diabetes or prediabetes.

Methods: An observational, analytical, cross-sectional study based on a retrospective analysis of 243 outpatients aged ≥ 18 years with hypertension and diabetes mellitus or prediabetes. Clinical, biochemical, and hemodynamic variables were analyzed, including high-sensitivity C-reactive protein (hs-CRP), cardiac index (CI), and systemic vascular resistance (SVR) measured by impedance cardiography. Carotid plaque was assessed using Doppler ultrasound. The association between FIBFAR (hs-CRP ≥ 2.5 mg/L, CI < 2.5 L/min/m², and SVR > 1600 dynes·s·cm⁻⁵) and carotid plaque was assessed using multivariate logistic regression.

Results: The median age was 58 years (IQR 49–67), and 64.0% were male. The prevalence of carotid plaque was 37.0%. The FIBFAR phenotype was present in 23.0% of the cohort and was independently associated with carotid plaque (OR 8.60; 95% CI: 4.39–17.70; $p < 0.001$), along with age ≥ 65 years (OR 1.94; 95% CI: 1.01–3.72; $p = 0.047$). The model showed appropriate calibration (Hosmer-Lemeshow $p = 0.374$) and moderate discriminatory power (AUC = 0.73; 95% CI: 0.66–0.79; $p < 0.001$).

Conclusions: In patients with cardiometabolic risk, the FIBFAR phenotype was independently associated with subclinical carotid atherosclerosis. Given the cross-sectional design, these findings should be interpreted as statistical associations and require prospective validation before their clinical application can be considered.

Key words: Hemodynamic phenotype – Inflammation – Impedance cardiography – Carotid atherosclerosis – Carotid plaque

RESUMEN

Introducción: La inflamación sistémica y las alteraciones hemodinámicas representan mecanismos fisiopatológicos complementarios involucrados en la enfermedad cardiovascular. La identificación de fenotipos integradores mediante herramientas no invasivas podría contribuir a una mejor caracterización de la aterosclerosis subclínica.

Objetivo: Evaluar la asociación entre el fenotipo hemodinámico-inflamatorio de bajo flujo y alta resistencia vascular sistémica (FIBFAR) y la presencia de placa carotídea en pacientes con riesgo cardiometabólico, definido por la presencia de hipertensión arterial y diabetes o prediabetes.

Material y métodos: Estudio observacional, analítico y transversal con análisis retrospectivo de 243 pacientes ambulatorios ≥ 18 años con hipertensión arterial y diabetes mellitus o prediabetes. Se analizaron variables clínicas, bioquímicas y hemodinámicas, incluyendo proteína C reactiva ultrasensible (PCR-us), índice cardíaco (IC) y resistencia vascular sistémica (RVS) mediante cardiografía por impedancia. La placa carotídea fue evaluada mediante ecografía Doppler. La asociación entre el FIBFAR (PCR-us $\geq 2,5$ mg/L, IC $< 2,5$ L/min/m² y RVS > 1600 dinas·s·cm⁻⁵) y placa carotídea se determinó mediante regresión logística multivariada.

Resultados: La mediana de edad fue de 58 años (RIC 49-67) y el 64,0% fueron varones. La prevalencia de placa carotídea fue del 37,0%. El fenotipo FIBFAR estuvo presente en el 23,0% de la cohorte y se asoció independientemente con placa carotídea (OR 8,60; IC95% 4,39-17,70; $p < 0,001$), junto con la edad ≥ 65 años (OR 1,94; IC95% 1,01-3,72; $p = 0,047$). El modelo mostró adecuada calibración (Hosmer-Lemeshow $p = 0,374$) y capacidad discriminativa moderada (AUC 0,73; IC 95% 0,66-0,79; $p < 0.001$).

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Correspondence: Paola Chong Velásquez. E-mail: dra.paolachong@gmail.com



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¹ Cardiology and Cardiovascular Imaging Department, Sanatorio Modelo de Caseros, Province of Buenos Aires, Argentina

² Noninvasive Vascular Laboratory, DIM Cardiovascular Prevention; Chair of Vascular Mechanics, Universidad Austral, Autonomous City of Buenos Aires, Argentina

³ Computer Systems and Data Analysis Specialist, Autonomous City of Buenos Aires, Argentina

Conclusiones: En pacientes con riesgo cardiometabólico, el fenotipo FIBFAR se asoció independientemente con aterosclerosis carotídea subclínica. Debido al diseño transversal, estos hallazgos deben interpretarse como asociaciones estadísticas y requieren validación prospectiva antes de considerar su aplicación clínica.

Palabras clave: Fenotipo hemodinámico – Inflamación - Cardiografía por impedancia - Aterosclerosis carotídea - Placa carotídea

INTRODUCTION

Atherosclerotic cardiovascular disease remains the leading cause of morbidity and mortality worldwide, and its burden is increasing in parallel with the rising prevalence of obesity, diabetes mellitus, dyslipidemia, and metabolic syndrome. (1,2) Although current risk stratification models incorporate traditional risk factors, a significant proportion of cardiovascular events occurs in individuals whose atherosclerotic burden is not fully explained by these determinants, prompting the search for biomarkers and phenotypes that integrate subclinical vascular risk. (3-5)

Low-grade chronic inflammation plays a central role in atherosclerosis, and high-sensitivity C-reactive protein (hs-CRP) has become established as a marker of residual inflammation and cardiovascular risk. (6-13) In parallel, hemodynamic abnormalities such as increased systemic vascular resistance (SVR) and reduced cardiac index are associated with vascular remodeling and progression of atherosclerotic disease and may be assessed noninvasively using impedance cardiography. (14-19)

Carotid ultrasound is a validated method for detecting atherosclerotic plaque, one of the markers of subclinical atherosclerosis with the greatest prognostic value. (20-24) However, inflammatory and hemodynamic mechanisms are typically studied separately.

Based on this, we propose the low-flow, high-systemic vascular resistance hemodynamic-inflammatory phenotype (FIBFAR), defined by hs-CRP ≥ 2.5 mg/L, cardiac index (CI) < 2.5 L/min/m², and SVR > 1600 dynes·s·cm⁻⁵, with these thresholds established *a priori* according to widely accepted physiological and clinical references. (12,13,18,25)

The combination of low-grade chronic inflammation (defined by hs-CRP ≥ 2.5 mg/L), reduced cardiac index (CI < 2.5 L/min/m²), and increased systemic vascular resistance (SVR > 1600 dynes·s·cm⁻⁵) represents a prespecified hemodynamic-inflammatory construct associated with a greater burden of subclinical carotid atherosclerosis in patients with cardiometabolic risk. Low-grade chronic inflammation and physical inactivity may promote endothelial dysfunction, increased vasoconstrictor tone and vascular resistance, ventricular-arterial uncoupling, and vascular remodeling.

OBJECTIVE

The objective of this study was to evaluate the association between the FIBFAR phenotype and the presence of subclinical carotid atherosclerosis in patients with cardiometabolic risk. Given the cross-sectional design of the study, the results were interpreted exclusively

in terms of association and do not allow causal relationships or predictive capacity to be established (Figure 1).

METHODS

Design and population

We conducted an observational, analytical, cross-sectional study based on a retrospective analysis of medical records of outpatients referred to the Cardiology Department of Sanatorio Modelo de Caseros (Buenos Aires, Argentina) between August 2024 and August 2025 for cardiometabolic risk assessment.

For the purposes of this study, cardiometabolic risk was operationally defined as the concomitant presence of hypertension and diabetes mellitus (or prediabetes), which were referral criteria for 100% of the cohort. The definition of both conditions is detailed in the section on clinical and biochemical variables. Although dyslipidemia, obesity, and metabolic syndrome were common in the study population (Table 1), they were not mandatory inclusion criteria.

A total of 243 patients aged 18 years or older were consecutively enrolled and underwent complete clinical, biochemical, hemodynamic, and carotid ultrasound evaluations.

Inclusion criteria

- Age ≥ 18 years.
- Concomitant diagnosis of hypertension and diabetes mellitus or prediabetes at the time of referral.
- Availability of high-sensitivity C-reactive protein (hs-CRP) testing.
- Hemodynamic assessment by impedance cardiography with measurement of cardiac index (CI) and systemic vascular resistance (SVR).
- Complete carotid Doppler ultrasound for the assessment of atherosclerotic plaque.

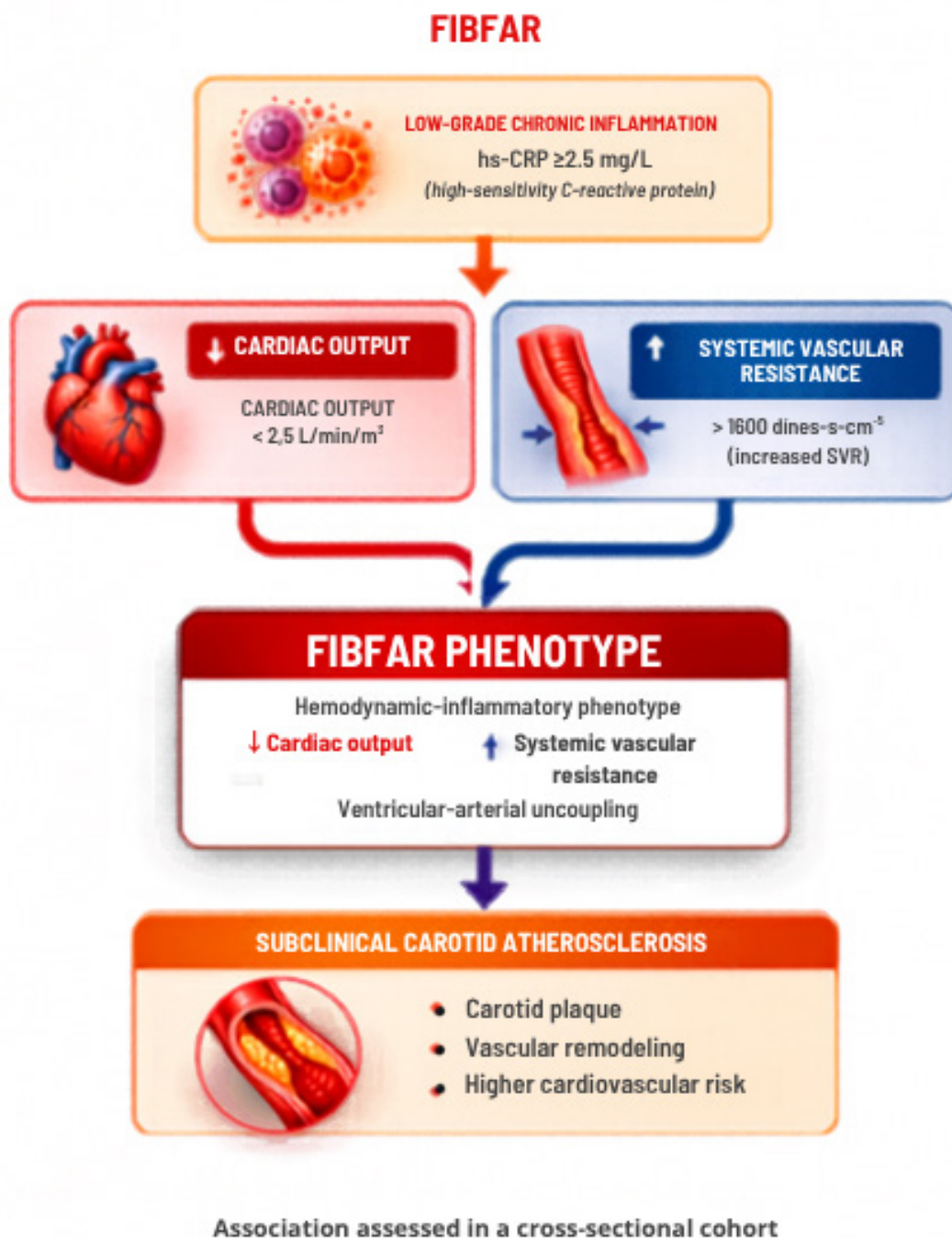
Exclusion criteria

- Incomplete clinical or biochemical data.
- Body mass index > 35 kg/m², due to technical limitations of impedance cardiography.
- Acute infectious processes, active systemic inflammatory diseases, or neoplasms undergoing active treatment.
- Cardiac arrhythmias, hemodynamic instability, or decompensated heart failure.
- Any other clinical condition that could significantly alter hemodynamic parameters or hs-CRP levels at the time of assessment.

Clinical and biochemical variables

Age, sex, and the main traditional cardiovascular risk factors were recorded. Hypertension was defined by a prior diagnosis or antihypertensive therapy. Diabetes mellitus was defined by a prior diagnosis, hypoglycemic therapy, or glycated hemoglobin (HbA1c) $\geq 6.5\%$. Dyslipidemia was defined by a prior diagnosis, lipid-lowering therapy, or low-density lipoprotein (LDL) cholesterol ≥ 160 mg/dL. Smoking was defined as current smoking or having quit within the past year. Obesity was defined by body mass index (BMI) ≥ 30 kg/m².

Fig. 1. Hypothetical pathophysiological framework of the FIBFAR hemodynamic-inflammatory phenotype



The figure was created using artificial intelligence.

Metabolic syndrome was defined according to the joint 2009 IDF/AHA/NHLBI criteria. (2)

In addition, drug therapy with potential anti-inflammatory or vasoactive effects (statins, renin-angiotensin system inhibitors, and antiplatelet agents) was recorded, as was estimated renal function using the CKD-EPI equation. These variables were considered potential confounding factors because of their known associations with systemic inflamma-

tion, hemodynamics, and carotid atherosclerosis, and were evaluated during construction of the multivariate model.

Biochemical measurements were performed after a 12-hour fast and included total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, HbA1c, creatinine, and hs-CRP. Pulse pressure was calculated as the difference between systolic blood pressure and diastolic blood pressure.

Hemodynamic assessment

Hemodynamic assessment was performed using impedance cardiography (Z-Logic® system, Exxer Ingeniería Electrónica, Buenos Aires, Argentina), a noninvasive technique validated against reference methods such as thermodilution and Doppler echocardiography and previously used for the assessment and management of patients with hypertension and heart failure. (18,19) Several studies have demonstrated good agreement between this method and these reference techniques for estimating cardiac output in various clinical settings.

Measurements were taken in the morning, after 10 minutes of rest in supine position, with caffeine consumption, smoking, and strenuous exercise avoided during the preceding 12 hours. The studies were performed by operators trained and experienced in impedance cardiography, following a standardized acquisition protocol recommended by the manufacturer.

CI (L/min/m²) and SVR (dynes·s·cm⁻⁵) values were recorded. The SVR cutoff point >1600 dynes·s·cm⁻⁵ was selected based on the upper limit of the physiological reference range (700–1600 dynes·s·cm⁻⁵) established in the literature and has previously been used to define elevated vascular resistance in clinical studies. (18,25,30–31)

No formal assessment of intraobserver or interobserver variability was performed in the present cohort. The reproducibility of the method is supported by previously published validation studies comparing it with thermodilution and Doppler echocardiography. (18,19)

Definition of hemodynamic-inflammatory phenotypes

The cutoff points used to define the phenotypes were established *a priori*, before the analysis of the database, based on pathophysiological principles and previously published clinical evidence, without deriving them from ROC curves or percentiles from the present cohort. This strategy aimed to preserve the reproducibility of the construct and avoid threshold optimization based on the observed results.

A CI <2.5 L/min/m² corresponds to the threshold used to define a low-flow state in impedance cardiography studies and previously published clinical algorithms. (18) A hs-CRP ≥2.5 mg/L falls within the range associated with increased inflammatory risk according to the AHA/CDC classification and is close to the threshold ≥2 mg/L used to define residual inflammatory risk in contemporary studies. (12,13,26,27) An SVR >1600 dynes·s·cm⁻⁵ corresponds to the upper limit of the physiological reference range (700–1600 dynes·s·cm⁻⁵) and was selected as an indicator of increased arterial afterload and elevated vascular resistance. (25,30–31)

These thresholds were not specifically developed for the assessment of subclinical carotid atherosclerosis. Therefore, the FIBFAR phenotype should be interpreted as a prespecified pathophysiological construct whose association with subclinical atherosclerosis requires confirmation in independent populations and prospective studies.

As an exploratory analysis, the performance of the individual components of the phenotype was subsequently evaluated using univariate ROC curves against the presence of carotid plaque. This analysis was purely exploratory and did not alter the initially defined cutoff points.

Four mutually exclusive hemodynamic-inflammatory phenotypes were defined:

- Adaptive phenotype: hs-CRP <2.5 mg/L, CI ≥2.5 L/min/m², and SVR ≤1600 dynes·s·cm⁻⁵.
- Vasoconstrictor inflammatory phenotype: hs-CRP ≥2.5 mg/L, CI ≥2.5 L/min/m², and SVR >1600 dynes·s·cm⁻⁵.

- FIBFAR (low-flow, high-resistance inflammatory phenotype): hs-CRP ≥2.5 mg/L, CI <2.5 L/min/m², and SVR >1600 dynes·s·cm⁻⁵.
- Indeterminate phenotype: patients who did not simultaneously meet the criteria for the preceding phenotypes.

Carotid atherosclerosis assessment

Carotid assessment was performed using Doppler ultrasound (Mindray Consona 7®, 7–14 MHz linear transducer), with bilateral examination of the common carotid artery, the carotid bulb, and the internal carotid artery. Operators experienced in vascular imaging performed the examinations in accordance with a standardized protocol for image acquisition and interpretation based on international recommendations for the ultrasound evaluation of carotid disease.

The presence of carotid plaque was defined according to the recommendations of the American Society of Echocardiography and the Mannheim Consensus as a focal thickening protruding into the arterial lumen or an intima-media thickness ≥1.5 mm in any carotid segment. (20,21)

Statistical Analysis

The analysis was performed using SPSS software v.28.0 (IBM Corp., Armonk, NY, USA), with a significance level of $\alpha = 0.05$ (two-sided).

Descriptive statistics: mean ± standard deviation (SD) was used for normally distributed variables or median and interquartile range (IQR) for non-normally distributed variables, and frequencies and percentages were used for categorical variables.

Inferential statistics: The Shapiro-Wilk test was used for normality. Group comparisons: Student's t-test or the Mann-Whitney U test was used to compare 2 groups and one-way ANOVA or the Kruskal-Wallis test for ≥3 groups. Repeated measures were assessed using ANOVA for repeated-measures or mixed linear models. Categorical associations were evaluated with the chi-square or Fisher's exact tests, and Pearson or Spearman coefficients were used for correlation.

Multivariate models: Multiple linear regression was performed to identify independent predictors of maximum Δ QTc. Multivariate binary logistic regression (stepwise method) was implemented to identify factors associated with the occurrence of MVA, including QT variability (dichotomized: QTV ≥15% vs. <15%), age, obesity, hypertension, and diabetes as covariates. Crude and adjusted odds ratios (OR) are reported with their 95% confidence intervals (95% CI). The goodness of fit was assessed using the Hosmer-Lemeshow test and Nagelkerke's.

Ethical Considerations

The protocol was approved by the Ethics Committee of the Sanatorio Modelo de Caseros. The requirement for informed consent was waived because anonymized data was used.

Statistical analysis

Clinical, biochemical, and hemodynamic characteristics were compared according to the presence of carotid plaque. Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), depending on their distribution as assessed by the Shapiro-Wilk test; categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

A univariate analysis was performed to identify varia-

bles associated with the presence of carotid plaque. Variables with predefined clinical relevance and/or univariate association ($p < 0.10$) were considered candidates for inclusion in a binary logistic regression model.

The multivariate model included the FIBFAR phenotype (primary exposure variable), age ≥ 65 years, sex, smoking status, body mass index, systolic blood pressure, HbA1c, HDL cholesterol, and diuretic use. Covariate selection combined prespecified clinical criteria with the results of the univariate analysis, prioritizing a parsimonious model and avoiding redundant or highly correlated variables. Hypertension and diabetes mellitus were not included as dichotomous variables because they were present in 100% of the cohort by definition of the inclusion criteria; their biological severity was represented by systolic blood pressure and HbA1c. Hs-CRP was not included as an independent covariate because it is a defining component of the FIBFAR phenotype, thereby avoiding collinearity.

With 90 events (presence of carotid plaque) and nine variables in the model, there were approximately 10 events per variable (EPV), which was considered adequate to minimize the risk of overfitting in binary logistic regression models.

Model calibration was assessed using the Hosmer-Lemeshow test, and its discriminatory ability was evaluated using the area under the ROC curve (AUC). Odds ratios (OR) with 95% confidence intervals (95% CI) were estimated, as well as sensitivity, specificity, positive predictive value, and negative predictive value at the optimal cutoff point. As an exploratory analysis, the individual diagnostic performance of hs-CRP, CI, and SVR was evaluated using univariate ROC curves. A p -value < 0.05 was considered statistically significant. All analyses were performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population characteristics

A total of 243 outpatients with cardiometabolic risk were included; all had hypertension and diabetes mellitus or prediabetes, in accordance with the predefined inclusion criteria. The median age was 58 years (IQR 49–67), and 64.0% were male.

The overall prevalence of carotid plaque was 37.0% (90/243). Table 1 shows the clinical, biochemical, and hemodynamic characteristics and concomitant drug therapy, stratified according to the presence of carotid plaque.

Patients with carotid plaque had a higher prevalence of smoking (62.2% vs. 47.1%; $p = 0.020$) and a larger hip circumference (89 vs. 85 cm; $p = 0.001$), with no significant differences in the prevalence of dyslipidemia (66.6% vs. 64.1%; $p = 0.900$) or in body mass index (32.0 vs. 30.9 kg/m²; $p = 0.080$). Note that, despite the high overall prevalence of dyslipidemia (66% in the cohort), it showed no association with the presence of carotid plaque, highlighting the independent contribution of the inflammatory and hemodynamic components of the FIBFAR phenotype.

From a biochemical and hemodynamic perspective, patients with plaque had higher values of HbA1c (7.4% vs. 6.9%; $p = 0.002$), hs-CRP (3.5 vs. 1.6 mg/L; $p = 0.001$), SVR (2250 vs. 2165 dynes·s·cm⁻⁵; $p = 0.012$), and pulse pressure (63 vs. 60 mmHg;

$p = 0.002$), together with lower CI (2.4 vs. 2.6 L/min/m²; $p = 0.009$) and HDL cholesterol levels (38 vs. 42 mg/dL; $p = 0.022$). No significant differences were observed in age, sex, LDL cholesterol, triglycerides, or left ventricular ejection fraction (LVEF).

Regarding concomitant drug therapy, the use of diuretics was more frequent among patients with carotid plaque (29% vs. 18%; $p = 0.043$). No significant differences were observed in the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, beta-blockers, statins, ezetimibe, fenofibrate, or sodium-glucose cotransporter 2 inhibitors.

Distribution of hemodynamic-inflammatory phenotypes

The distribution of the four hemodynamic-inflammatory phenotypes is shown in Table 2. The most common phenotype was the indeterminate phenotype (131 patients; 53.9%), followed by the FIBFAR phenotype (56; 23.0%), the inflammatory vasoconstrictor phenotype (32; 13.2%), and the adaptive phenotype (24; 9.9%).

The prevalence of carotid plaque differed significantly across the various phenotypes (overall χ^2 ; $p < 0.001$). The FIBFAR phenotype (low-flow, high-resistance inflammatory phenotype) had the highest proportion of patients with carotid plaque (75.0%), followed by the inflammatory vasoconstrictor phenotype (56.2%), while the lowest prevalences were observed in the adaptive phenotype (25.0%) and the indeterminate (18.5%) phenotype.

Sensitivity analysis of cutoff points

The CI showed modest discriminatory power (AUC = 0.60), and the optimal cutoff point determined by the Youden index was 2.5 L/min/m², exactly matching the threshold used to define the phenotype.

Hs-CRP showed moderate discriminatory power (AUC = 0.70), with a population median of 2.7 mg/L and an optimal cutoff point of 3.2 mg/L. This value was slightly higher than the 2.5 mg/L predefined threshold, suggesting that the selected cutoff point prioritizes sensitivity over specificity for identifying residual inflammation.

SVR showed the lowest individual discriminatory power (AUC = 0.60). The optimal cutoff point according to the Youden index was 2235 dynes·s·cm⁻⁵, higher than the 1600 dynes·s·cm⁻⁵ prespecified value, which corresponds to the upper limit of the physiological reference range. These findings suggest that SVR alone has limited ability to discriminate the presence of carotid plaque in this cohort.

However, the simultaneous combination of elevated systemic inflammation, low cardiac index, and increased SVR in the FIBFAR composite phenotype showed a considerably stronger association with the presence of carotid plaque (adjusted OR 8.60; 95% CI: 4.39–17.70) than any of its components evaluated individually, supporting the hypothesis that integrating these domains provides complementary information.

Table 1. Clinical, biochemical, and hemodynamic characteristics and concomitant drug therapy according to the presence of carotid plaque

Variable	With plaque (n = 90)	Without plaque (n = 153)	p
Age, years, median (IQR)	60 (52–67)	57 (52–65)	0.200
Male sex, n (%)	58 (64.4)	85 (55.6)	0.200
Smoking, n (%)	56 (62.2)	72 (47.1)	0.020
Dyslipidemia, n (%)	59 (66.6)	98 (64.1)	0.900
BMI, kg/m ² , median (IQR)	32 (28.7–33.9)	30.9 (28.1–33.7)	0.080
Hip circumference, cm, median (IQR)	89 (84–101)	85 (77–89)	0.001
SBP, mmHg, median (IQR)	140 (134–146)	140 (124–145)	0.018
LDL-C, mg/dL, median (IQR)	100 (74–123)	110 (84–140)	0.120
HDL-C, mg/dL, median (IQR)	38 (34–45)	42 (36–54)	0.022
Triglycerides, mg/dL, median (IQR)	145 (137–187)	168 (116–211)	0.400
HbA1c, %, median (IQR)	7.4 (6.8–7.5)	6.9 (6.4–7.5)	0.002
hs-CRP, mg/L, median (IQR)	3.5 (2.6–5.9)	1.6 (0.85–3.45)	0.001
LVEF, %, median (IQR)	65.5 (58–68)	63 (58–68)	0.500
Cardiac index, L/min/m ² , median (IQR)	2.4 (2.2–2.6)	2.6 (2.2–3.4)	0.009
SVR, dynes·s·cm ⁻⁵ , median (IQR)	2,250 (1,182–2,613)	2,165 (1,238–2,551)	0.012
Pulse pressure, mmHg, median (IQR)	63 (59–64)	60 (45–64)	0.002
Concomitant drug therapy, n (%)			
ACE inhibitors	19 (21.1)	38 (24.8)	0.500
ARAs	63 (70.0)	105 (68.6)	0.900
Calcium channel blockers	36 (40.0)	52 (34.0)	0.400
Beta-blockers	40 (44.4)	77 (50.5)	0.300
Diuretics	26 (28.9)	27 (17.6)	0.043
Aldosterone antagonists	0 (0.0)	1 (0.7)	0.990
Statins	59 (65.6)	101 (66.0)	0.900
Ezetimibe	3 (3.3)	10 (6.6)	0.400
Fenofibrates	10 (11.1)	14 (9.2)	0.600
SGLT2 inhibitors	35 (39.9)	52 (34.0)	0.500

ACE inhibitors: angiotensin-converting enzyme inhibitors; ARAs: angiotensin II receptor antagonists; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; SGLT2: sodium-glucose cotransporter 2; SVR: systemic vascular resistance. Comparisons were performed using the Mann-Whitney test for continuous variables or the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Table 2. Distribution of hemodynamic-inflammatory phenotypes and prevalence of carotid plaque

Phenotype	n (%)	Carotid plaque, n (%)
Adaptive	24 (9.9)	6 (25.0)
Inflammatory vasoconstrictor	32 (13.2)	18 (56.2)
FIBFAR	56 (23.0)	42 (75.0)
Indeterminate	131 (53.9)	24 (18.5)
Total	243 (100)	90 (37.0)

FIBFAR: low-flow, high-resistance inflammatory phenotype.

Overall χ^2 test for the association between phenotype and plaque: $p < 0.001$.

Multivariate analysis

In the multivariate logistic regression analysis (Table 3), adjusted for smoking status, sex, body mass index, systolic blood pressure, HbA1c, HDL cholesterol, and diuretic use, the FIBFAR hemodynamic-inflammatory phenotype was independently associated with the presence of carotid plaque (OR 8.60; 95% CI: 4.39–17.70; $p < 0.001$). Age ≥ 65 years was also independently associated with carotid plaque (OR 1.94; 95% CI: 1.01–3.72; $p = 0.047$), while none of the remaining covariates reached statistical significance. It is worth noting that dyslipidemia, despite its high prevalence in the cohort (66%), was not included in the multivariate model because it did not show a significant association in the univariate analysis ($p = 0.90$), which reinforces the independent contribution of the FIBFAR phenotype beyond traditional lipid risk factors.

The model demonstrated adequate calibration, as evidenced by the Hosmer-Lemeshow test ($p = 0.374$), and moderate discriminatory power (AUC = 0.73; 95% CI: 0.66–0.79; $p < 0.001$; Figure 2). At the optimal cut-

off point, sensitivity was 65% and specificity was 73%. Considering the prevalence of carotid plaque observed in the cohort (37%), the positive predictive value was 58.6% and the negative predictive value was 78.0%.

DISCUSSION

In this observational cross-sectional study, the FIBFAR hemodynamic-inflammatory phenotype was independently associated with the presence of sub-clinical carotid atherosclerosis in patients with cardio-metabolic risk, even after adjusting for age and other potential confounding factors. The magnitude of the observed association (adjusted OR 8.60) suggests that the integration of systemic inflammation and hemodynamic abnormalities may reflect a biological profile associated with a higher atherosclerotic burden. Given the cross-sectional design, these findings should be interpreted exclusively as statistical associations and do not allow causal or temporal relationships or predictive capacity to be established.

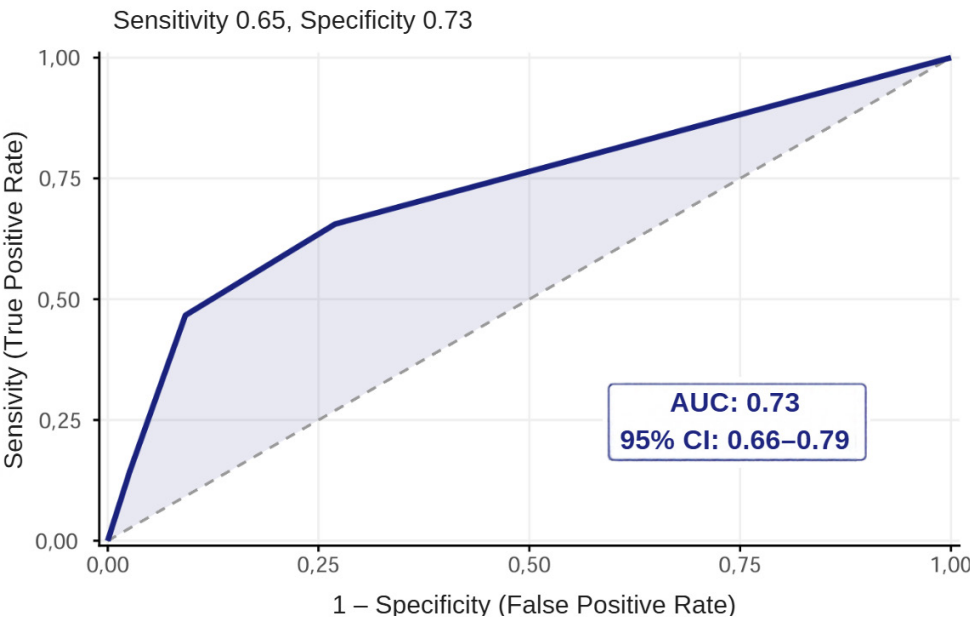
The multivariate model showed moderate discrim-

Table 3. Multivariate logistic regression model for predicting carotid plaque

Variable	OR	95% CI	p
FIBFAR	8.6	4.39–17.70	<0.001
Age ≥ 65 years	1.94	1.01–3.72	0.047

95% CI: 95% confidence interval; OR: odds ratio. The model was adjusted for smoking status, sex, BMI, systolic blood pressure, HbA1c, HDL cholesterol, and diuretic use; none of these covariates showed a significant independent association in the final model. The model included nine variables and 90 events, corresponding to 10 events per variable.

Fig. 2. ROC curve of the multivariate model for predicting carotid plaque



inatory power ($AUC = 0.73$) and adequate calibration, supporting the internal consistency of the proposed phenotype. Although no formal comparison was made with traditional cardiovascular risk stratification models, this performance is comparable to that reported in studies integrating inflammatory biomarkers and arterial stiffness parameters. (28,29)

Our findings are consistent with the high prevalence of subclinical atherosclerosis described in patients with cardiometabolic risk in the PESA study, (22) as well as with the prognostic value of carotid plaque demonstrated in the ARIC and MESA cohorts. (23,24) Unlike those studies, which evaluated inflammatory and hemodynamic components independently, the present study proposes a pathophysiological construct that integrates both domains into a single clinical phenotype.

The cutoff points used to define FIBFAR were established *a priori* based on pathophysiological principles and previously published clinical evidence, rather than through statistical optimization within the cohort. (12,13,18,25) Exploratory analysis showed a higher prevalence of carotid plaque when elevated systemic inflammation, low CI, and increased SVR coexisted, compared with the isolated presence of each of these components.

From a pathophysiological perspective, low-grade chronic inflammation and physical inactivity have been associated with endothelial dysfunction, reduced nitric oxide bioavailability, and increased vasoconstrictor tone—phenomena considered early events in the atherogenic cascade. This process may contribute to increased SVR, arterial stiffness, and, subsequently, ventricular-arterial uncoupling and vascular remode-

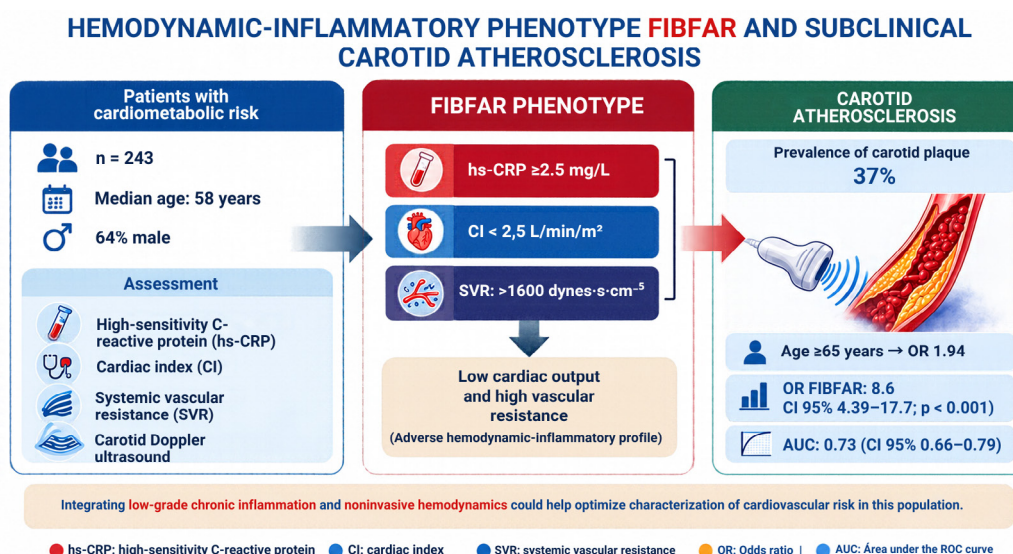
ling. (6–9, 14–17) In this context, FIBFAR represents a clinical manifestation of the coexistence of residual inflammation and hemodynamic abnormalities potentially mediated, at least in part, by endothelial dysfunction. Although the present study design does not allow us to demonstrate that these mechanisms directly explain the presence of carotid plaque, the observed results are consistent with the pathophysiological model described in the literature.

It is relevant to note that dyslipidemia, despite its high prevalence in the cohort (66%), was not significantly associated with the presence of carotid plaque in the univariate analysis ($p = 0.90$), whereas the FIBFAR phenotype remained strongly and independently associated with carotid plaque ($OR = 8.60$, $p = 0.001$). This finding suggests that the integration of inflammatory and hemodynamic parameters could provide complementary information to traditional lipid risk factors.

The weak positive correlation between SVR and hs-CRP ($p = 0.37$; $p < 0.001$) suggests that both components represent partially independent pathophysiological dimensions within the FIBFAR phenotype, supporting their integration into a composite construct.

From a clinical standpoint, the combination of impedance cardiography and hs-CRP represents a completely noninvasive strategy that could potentially be applied in the outpatient setting. If confirmed in prospective studies, identification of the FIBFAR phenotype could help select patients with a higher subclinical atherosclerotic burden who may be candidates for more intensive evaluation or therapeutic strategies targeting both residual inflammatory risk and hemodynamic abnormalities. (30,31)

Graphical abstract



Limitations

The main limitations stem from the cross-sectional design, which does not allow causal relationships or predictive capacity to be established. The cohort was single-center and included exclusively patients with hypertension and diabetes mellitus or prediabetes, which may limit the generalizability of the findings. The cutoff points used to define the FIBFAR phenotype were established according to pathophysiological principles and previous clinical evidence; however, they require specific validation in independent populations. Finally, intraobserver and interobserver reproducibility of impedance cardiography was not assessed in this cohort, although this technique has been previously validated against reference methods. (18,19)

CONCLUSIONS

In this cohort of patients with cardiometabolic risk, the FIBFAR hemodynamic-inflammatory phenotype was independently associated with the presence of subclinical carotid atherosclerosis. These findings suggest that the integration of inflammatory and hemodynamic parameters could provide complementary information for characterizing vascular risk. However, given the cross-sectional design, causal relationships and predictive capacity cannot be established. Validation of the FIBFAR phenotype requires prospective, multicenter studies evaluating its reproducibility, association with cardiovascular events, and potential clinical utility.

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Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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