

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

Selective dysfunction of e-series inflammation resolution in diabetes: the e-series resolution dysfunction index as a novel biomarker in chronic coronary syndrome

Authors: Beata Krasieńska, Tomasz Urbanowicz, Ewelina Grywalska, Maciej Kurpierz, Andrzej Tykarski

Article type/Research letter

Received: June 18, 2026.

Revision accepted: July 3, 2026.

Published online: July 7, 2026.

ISSN: 1897-9483

Pol Arch Intern Med.

doi:10.20452/pamw.17343

This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License ([CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)), allowing anyone to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, including commercial purposes, provided the original work is properly cited.

Selective dysfunction of e-series inflammation resolution in diabetes: the e-series resolution dysfunction index as a novel biomarker in chronic coronary syndrome

Beata Krasińska^{1*}, Tomasz Urbanowicz^{2*}, Ewelina Grywalska³, Maciej Kurpisz⁴, Andrzej Tykarski¹

1 Department of Hypertensiology, Angiology, and Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland

2 Department of Cardiac Surgery and Transplantology, Poznan University of Medical Sciences, Poznań, Poland

3 Department of Experimental Immunology, Medical University of Lublin, Lublin, Poland

4 Institute of Human Genetics, Polish Academy of Sciences, Poznań, Poland

* BK and TU contributed equally to this work.

Correspondence to: Tomasz Urbanowicz, MD, Associate Professor, Department of Cardiac Surgery and Transplantology, Poznan University of Medical Sciences, ul. Długa 1/2, 61-848 Poznan, Poland, phone: +48 61 854 9210, email: turbanowicz@ump.edu.pl

Introduction

The association between type 2 diabetes mellitus and chronic low-grade inflammation is well established and is considered a major contributor to accelerated atherosclerosis and adverse cardiovascular outcomes [1]. Hyperglycemia, insulin resistance, and metabolic stress promote sustained activation of innate immune pathways, endothelial dysfunction, and vascular injury [2]. Traditionally, these processes have been interpreted primarily through the paradigm of

excessive inflammatory activation [3,4]. However, this framework may only partially explain the persistence of inflammation in diabetes.

Inflammation resolution is an active, highly regulated process rather than a passive decline [5]. Successful resolution requires coordinated activation of endogenous pathways that terminate leukocyte recruitment, promote clearance of inflammatory cells and debris, and restore tissue homeostasis. Specialized pro-resolving mediators (SPMs), biosynthesized from omega-3 polyunsaturated fatty acids, are central regulators of these processes [6].

Among the best-characterized SPMs is resolvin E1 (RvE1), an eicosapentaenoic acid (EPA)-derived mediator that limits neutrophil trafficking, suppresses pro-inflammatory signaling, and facilitates the restoration of tissue homeostasis [7]. In contrast, docosahexaenoic acid (DHA)-derived mediators, including resolvin D1 (RvD1) and maresin-1 (MaR1), predominantly participate in later phases of resolution by enhancing efferocytosis, tissue repair, and the restoration of tissue integrity [8].

Although alterations in individual pro-resolving mediators have been reported in metabolic disorders, available data remain limited and often inconsistent. Importantly, previous studies have largely focused on isolated mediators rather than on the balance between distinct resolution pathways. Consequently, it remains unclear whether diabetes is associated with generalized impairment of inflammation resolution or with selective dysfunction of specific pro-resolving programs.

We therefore hypothesized that diabetes does not uniformly impair inflammation resolution but instead induces selective dysfunction of the EPA-derived E-series pathway while relatively preserving, or even compensatorily activating, DHA-derived resolution programs. Consequently, biological divergence between these pathways, rather than the absolute concentration of any individual mediator, may better characterize diabetes-associated resolution dysfunction.

Patients and methods

This prospective observational study included 89 consecutive patients referred for evaluation of chronic coronary syndrome. All patients underwent standard clinical assessment, transthoracic echocardiography, and coronary angiography. Thirty-one patients had established type 2 diabetes mellitus, and 58 had no history of diabetes. Type 2 diabetes mellitus was defined as a prior diagnosis established by a diabetologist according to contemporary diagnostic criteria and present for at least one year before enrollment. Patients with unstable angina, previous cardiovascular interventions, and concomitant at least moderate valvular pathology were excluded from the study.

Measurement of lipid mediators

Blood samples were obtained before coronary angiography. Circulating concentrations of LTB₄, RvE1, RvD1, MaR1, and PGE₂ were measured using commercially available enzyme-linked immunosorbent assays according to the manufacturers' instructions. Laboratory personnel were blinded to clinical data.

Development of the E-Series Resolution Dysfunction Index

To explore potential imbalances among major pro-resolving pathways, we prespecified an exploratory composite measure, the E-Series Resolution Dysfunction Index (ERDI). Because our objective was to evaluate relative divergence within the resolution network rather than inflammatory burden itself, ERDI was calculated as:

$$\text{ERDI} = (\text{RvD1} + \text{MaR1}) / \text{RvE1}$$

The rationale for ERDI was based not only on the distinct biosynthetic origins of the analyzed mediators but also on their complementary biological roles within the inflammation-resolution network. RvE1 represents the principal circulating mediator of the EPA-derived E-series pathway, which primarily regulates early counter-inflammatory signaling by limiting neutrophil recruitment and inflammatory amplification. In contrast, RvD1 and MaR1 are major

DHA-derived mediators that are predominantly involved in downstream resolution, macrophage reprogramming, efferocytosis, and tissue repair. Consequently, ERDI was designed to quantify the relative predominance of downstream DHA-derived resolution activity over upstream E-series resolution capacity rather than the absolute concentration of individual mediators.

Alternative composite formulations were considered during conceptual development; however, the final ERDI was selected a priori because it directly reflects biological rationale.

Statistical analysis

Detailed information regarding the applied statistical analysis is presented in Supplementary material, *Statistical analysis*.

Ethics

The study was approved by the Institutional Ethics Committee of Poznan University of Medical Sciences (protocol code 113/21; November 6, 2021). Written informed consent was obtained from all participants.

Results

Study population and clinical characteristics

Baseline demographic and clinical characteristics, laboratory test results (including fasting glucose and glycemic hemoglobin), coronary angiography findings, and estimated left ventricular ejection fraction were similar between groups and are presented in Supplementary material, *Table S1*. No significant differences in pharmacotherapy (also diabetic) were observed after correction for multiple comparisons (Supplementary material, *Table S2*).

Measurement of lipid mediators

Compared with non-diabetic individuals, diabetic patients demonstrated significantly higher concentrations of LTB₄ ($P < 0.001$; $FDR Q < 0.001$), RvD1 ($P < 0.001$; $FDR Q < 0.001$), and

MaR1 ($P < 0.001$; $FDR Q < 0.001$), and significantly lower concentrations of RvE1 ($P < 0.001$; $FDR Q < 0.001$). PGE2 concentrations did not differ between groups ($P = 0.19$) (Supplementary material, *Table S3*). The potential correlations between lipid mediators and laboratory findings, including peripheral blood analysis, kidney function, lipidogram, and glucose homeostasis parameters, were insignificant, as assessed using Spearman's rho tests (*Table S4*). Lower RvE1, together with higher RvD1 and MaR1, resulted in marked ERDI elevation. Median ERDI was approximately threefold higher in patients with diabetes than in those without diabetes (124.80 [88.28-163.31] vs 42.85 [16.69-71.13], $P < 0.001$; $FDR Q < 0.001$).

In multivariable analysis, ERDI remained independently associated with diabetes after adjustment for relevant clinical covariates (OR 1.03; 95% CI 1.02–1.05; $P < 0.001$) (Supplementary material, *Table S5*). ERDI demonstrated higher discriminatory performance than individual mediators (AUC 0.88), consistent with the hypothesis that pathway integration better reflects the biology of resolution than isolated lipid mediators (Supplementary material, *Table S6*, *Figure 1C*). In paired comparisons, ERDI significantly outperformed RvD1, MaR1, LTB4, and PGE2, while showing a non-significant trend toward better discrimination than RvE1 (Supplementary material, *Table S7*). ROC curves are presented in Supplementary material, *Figure S1*.

In the next step, internal bootstrap validation with 2000 resamples confirmed the stable discriminatory performance of ERDI, with apparent AUCs of 0.88 and 0.88 after optimism correction, as presented in Supplementary material, *Table S8*. The addition of ERDI to the clinical model significantly improved the characterization of the diabetes-associated inflammation-resolution phenotype, increasing the AUC from 0.67 to 0.88 ($\Delta AUC = 0.21$; DeLong $P = 0.002$). Reclassification metrics confirmed incremental value, with continuous $NRI = 1.09$ and $IDI = 0.30$, both $P < 0.001$ (Supplementary material, *Table S9*).

Discussion

The principal finding indicates that patients with diabetes exhibited a distinct pattern of inflammation-resolution biology characterized by lower circulating concentrations of RvE1 despite higher concentrations of RvD1 and MaR1 [9]. These observations suggest selective impairment of the E-series resolution pathway rather than generalized suppression of pro-resolving mechanisms [10]. ERDI was intentionally constructed to reflect the biological organization of the inflammation-resolution network. Although RvE1, RvD1, and MaR1 all belong to the family of specialized pro-resolving mediators, they do not represent interchangeable anti-inflammatory molecules. Instead, they occupy distinct regulatory levels within the resolution cascade and orchestrate different phases of the host response to inflammatory injury.

RvE1, an EPA-derived E-series mediator, functions predominantly as an upstream regulator of inflammatory amplification. By antagonizing leukotriene B4 signaling through BLT1, limiting neutrophil recruitment, reducing leukocyte-endothelial interactions, and attenuating pro-inflammatory cytokine production, RvE1 restrains the early propagation of inflammation before extensive tissue injury develops. Consequently, reduced RvE1 should not be interpreted simply as a lower concentration of a single lipid mediator but rather as impaired activity of one of the principal regulatory mechanisms responsible for terminating excessive inflammatory activation. Within this conceptual framework, the denominator of ERDI represents the functional capacity of the E-series pathway to control inflammatory escalation.

In contrast, RvD1 and MaR1 are DHA-derived mediators whose predominant biological actions occur during later phases of resolution. Both molecules promote macrophage polarization toward a pro-resolving phenotype, stimulate efferocytosis of apoptotic neutrophils, facilitate clearance of cellular debris, suppress persistent inflammatory signaling, and promote restoration of tissue integrity. Importantly, increased circulating concentrations of these

mediators should not be interpreted as evidence of enhanced anti-inflammatory protection. Rather, under conditions of chronic metabolic inflammation such as diabetes, increased RvD1 and MaR1 may represent activation of compensatory repair programs attempting to restore tissue homeostasis despite inadequate upstream control of inflammatory propagation.

The concept that persistent inflammation may result not only from excessive inflammatory activation but also from defective resolution has gained increasing attention in recent years [11]. Our findings extend this concept to diabetes by demonstrating divergence among major resolution pathways.

This distinction may have important biological implications. If diabetes were associated with a generalized failure of inflammatory resolution, reductions would be expected across multiple classes of specialized pro-resolving mediators [12]. In contrast, the simultaneous decrease in RvE1 and the increases in both RvD1 and MaR1 observed in the present study point toward pathway-specific regulation. Such divergence suggests distinct resolution programs respond differently to the diabetic inflammatory milieu.

The mechanisms underlying the reduction in circulating RvE1 concentrations cannot be determined in the present study. Several mechanisms may contribute to reduced circulating RvE1, including altered EPA metabolism, increased mediator consumption during persistent inflammation, impaired biosynthesis, or altered receptor signaling. Although these mechanisms cannot be distinguished in the present study, the observed profile supports selective vulnerability of the E-series pathway. Consequently, ERDI should be interpreted as a marker of relative pathway divergence rather than a measure of inflammatory burden.

The principal value of ERDI, therefore, lies not in identifying diabetes itself but in biologically phenotyping diabetic patients according to the integrity of endogenous inflammation-resolution pathways. If validated, such biological phenotyping may support

cardiovascular risk stratification, identification of residual inflammatory risk, monitoring of therapeutic response, or future selection of patients for resolution-targeted interventions.

Limitations

Several limitations should be acknowledged. First, the study population was relatively small, which limits statistical power and increases susceptibility to random variation. Second, the cross-sectional design precludes conclusions regarding causality or temporal relationships between diabetes and alterations in resolution pathways. Third, lipid mediators were quantified using ELISA rather than LC-MS/MS. Because specialized pro-resolving mediators circulate at very low concentrations, immunoassays may exhibit cross-reactivity with structurally related lipids; therefore, absolute concentrations should be interpreted with caution. Nevertheless, all samples were processed under identical analytical conditions, supporting the validity of relative comparisons between groups. Fourth, dietary intake of omega-3 fatty acids, and other factors that may influence mediator concentrations were not systematically assessed. Fifth, Information regarding diabetes duration, chronic microvascular complications, and cumulative exposure to contemporary glucose-lowering therapies was not uniformly available, precluding assessment of their potential influence on inflammation-resolution pathways. Finally, ERDI represents an exploratory biologically derived index and requires validation in independent cohorts before any clinical application can be considered.

From a translational perspective, the ROC analyses should be interpreted as evidence supporting the biological coherence of the proposed index rather than its clinical utility for diagnosing diabetes. Because diabetes diagnosis is already well established using standard biochemical criteria, the principal significance of ERDI lies in its ability to quantify pathway-specific resolution dysfunction and thereby provide mechanistic insight into the inflammatory phenotype associated with diabetes.

Whether similar pathway-specific alterations occur in diabetic patients without established coronary artery disease, during acute coronary syndromes, or across broader metabolic populations remains unknown and requires dedicated external validation.

Conclusions

Rather than indicating generalized failure of inflammation resolution, our findings support selective dysregulation of the EPA-derived E-series pathway with relative preservation of DHA-derived resolution programs. ERDI provides a biologically informed measure of this pathway disequilibrium, reflecting impaired upstream E-series regulation relative to compensatory downstream DHA-derived resolution activity. These findings support the concept that pathway-specific resolution biology, rather than individual lipid mediator concentrations, may better characterize inflammation-resolution dysfunction in diabetes and warrant validation of ERDI as a mechanistic biomarker in independent cohorts.

Article information

Acknowledgments: None.

Funding: None declared.

Conflict of interest: None declared.

AI statement: Artificial intelligence–assisted writing tools (ChatGPT, OpenAI, and Grammarly) were used exclusively for language editing and manuscript organization. They did not contribute to the study design, interpretation of results, or scientific conclusions.

Open access: This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing anyone to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, including commercial purposes, provided the original work is properly cited.

How to cite: Krasieńska B, Urbanowicz T, Grywalska E, et al. Selective dysfunction of e-series inflammation resolution in diabetes: the e-series resolution dysfunction index as a novel biomarker in chronic coronary syndrome. *Pol Arch Intern Med.* 2026; XX: 17343. doi:10.20452/pamw.17343

References

1. Ye J, Li L, Wang M, et al. Diabetes mellitus promotes the development of atherosclerosis: the role of NLRP3. *Front Immunol.* 2022; 12: 900254.
2. Zhao L, Yuan J, Yang Q, et al. Diabetes and its complications: molecular mechanisms, prevention and treatment. *Signal Transduct Target Ther.* 2026; 11: 22-49.
3. Pruc M, Kubica J, Banach M et al. Diagnostic and prognostic performance of the neutrophil-to-lymphocyte ratio in acute coronary syndromes: a meta-analysis of 90 studies including 45 990 patients. *Pol Heart J.* 2024; 82: 276–284.
4. Natorska J, Ząbczyk M, Undas A. Neutrophil extracellular traps (NETs) in cardiovascular diseases: From molecular mechanisms to therapeutic interventions. *Pol Heart J.* 2023; 81: 1205–1216.
5. Li C, Wang Z, Yang Y, et al. Pro-resolving lipid mediators in diseases: exploring the molecular basis and clinical implication. *Mol Biomed.* 2026; 7: 1-48.
6. Al-Shaer AE, Buddenbaum N, Shaikh SR. Polyunsaturated fatty acids, specialized pro-resolving mediators, and targeting inflammation resolution in the age of precision nutrition. *Biochim Biophys Acta Mol Cell Biol Lipids.* 2021; 1866: 158936-158956.
7. Duvall MG, Levy BD. DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation. *Eur J Pharmacol.* 2016; 785: 144-155.

8. Chiurchiù V, Leuti A, Dalli J, et al. Proresolving lipid mediators resolvin D1, resolvin D2, and maresin 1 are critical in modulating T cell responses. *Sci Transl Med.* 2016; 8: 353ra111-353ra135.
9. Sugimoto MA, Sousa LP, Pinho V, et al. Resolution of Inflammation: What Controls Its Onset? *Front Immunol.* 2016; 7: 160-178.
10. Al-Shaer AE, Pal A, Shaikh SR. Resolvin E1-ChemR23 axis regulates the hepatic metabolic and inflammatory transcriptional landscape in obesity at the whole genome and exon level. *Front Nutr.* 2021; 8: 799492-799507.
11. Bender EC, Tareq HS, Suggs LJ. Inflammation: a matter of immune cell life and death. *NPJ Biomed Innov.* 2025; 2: 7-16.
12. Hellmann J, Tang Y, Kosuri M, et al. Resolvin D1 decreases adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice. *FASEB J.* 2011; 25: 2399-23407.

Incremental discrimination by ERDI

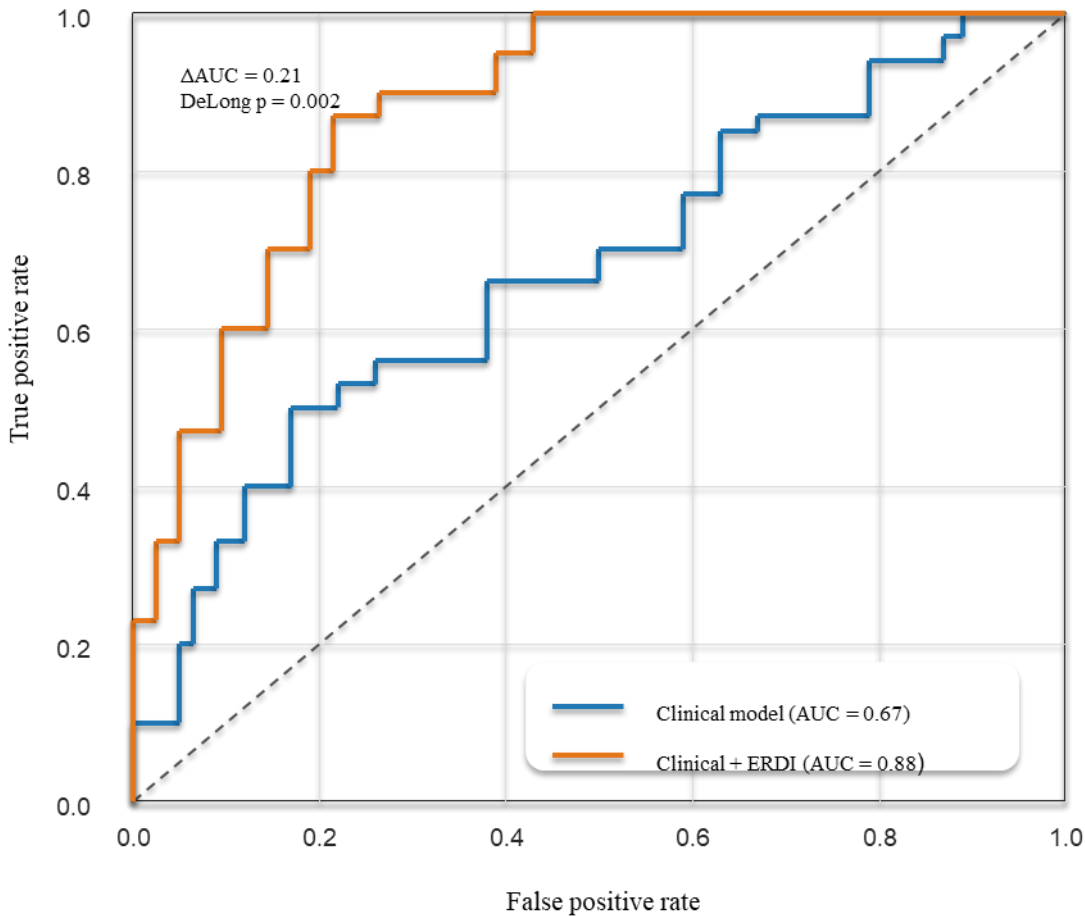


Figure 1 Incremental discrimination of ERDI beyond conventional clinical variables. Receiver-operating characteristic (ROC) curves comparing a clinical model (age, sex, obesity, hypertension, serum creatinine concentration, and coronary artery disease) with the same model supplemented by the E-Series Resolution Dysfunction Index (ERDI) for the identification of diabetes. Addition of ERDI significantly improved discrimination, increasing the area under the curve (AUC) from 0.67 to 0.88 ($\Delta\text{AUC} = 0.21$; DeLong $P = 0.002$). Reclassification analyses further demonstrated incremental predictive value (continuous net reclassification improvement [NRI] = 1.09; integrated discrimination improvement [IDI] = 0.30; both $P < 0.001$).

Short title: Lipid mediators and diabetes mellitus