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Reply to the Letter to the Editor: "Stress Hyperglycemia Ratio is Associated with Intracardiac Thrombus in Acute Ischemic Stroke"

Editöre Mektup Yanıtı: Akut İskemik İnmede Stres Hiperglisemi Oranı ile İntrakardiyak Trombüs Arasındaki İlişki

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

Vedat Çiçek[1,2]
Almina Erdem[3]
Ezgi Hasret Kozan Çıkırıkçı[4]
İrem Yılmaz[3]
Elif Günhan[3]
Emrecan Uygun[3]
Salih Karaismail[5]
Mehmet Uzun[3]
Mert İlker Hayıroğlu[6]
Ahmet Lütfullah Orhan[3]
Tufan Çınar[7]

[1]Department of Radiology, Machine & Hybrid Intelligence Lab, Northwestern University, Chicago, IL, United States
[2]Tatvan State Hospital, Bitlis, Türkiye
[3]Department of Cardiology, Sultan II. Abdulhamid Han Training and Research Hospital, Health Sciences University, İstanbul, Türkiye
[4]Department of Public Health Nursing, Koç University School of Nursing, İstanbul, Türkiye
[5]Department of Neurology, Sultan II. Abdulhamid Han Training and Research Hospital, Health Sciences University, İstanbul, Türkiye
[6]Department of Cardiology, Dr. Siyami Ersek Cardiovascular and Thoracic Surgery Research and Training Hospital, İstanbul, Türkiye
[7]School of Medicine, University of Maryland, Baltimore, USA

Corresponding author:
Vedat Çiçek
✉ vedatacicek@gmail.com

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To the Editor,

The correspondence raises three important points regarding the biological mechanisms and methodology underlying intracardiac thrombus formation in acute ischemic stroke (AIS). We address each point in turn.[1]

Stress Hyperglycemia as an Integrated Metabolic–Inflammatory Signal

The stress hyperglycemia ratio (SHR) is not solely a prothrombotic index. Relative hyperglycemia during acute illness reflects a broader neuroendocrine and inflammatory response, including catecholamine and cortisol surges, insulin resistance, and cytokine activation.[2,3] This is one reason why SHR may serve as a useful biomarker: it integrates multiple converging pathways rather than isolating a single mechanism. However, the data indicate that this integrative signal is not fully captured by systemic inflammation alone. In the same multivariable model, C-reactive protein (CRP) and SHR each retained an independent association with intracardiac thrombus.[4] (Adjusted odds ratio [OR] for SHR, 2.39; 95% CI, 1.11–5.17; P = 0.027; adjusted OR for CRP, 1.015; 95% CI, 1.009–1.021; P < 0.001.) Their retention after mutual adjustment indicates that metabolic stress and inflammation act as partially independent, complementary contributors to thrombogenesis rather than one serving as a proxy for the other. This finding is mechanistically coherent: acute dysglycemia promotes endothelial dysfunction through oxidative stress and reduced nitric oxide bioavailability, enhances platelet activation and tissue factor–mediated coagulation, and impairs fibrinolysis by increasing plasminogen activator inhibitor-1 levels.[5]

The Atrial Substrate and Atrial Cardiomyopathy

The high prevalence of paroxysmal atrial fibrillation (PAF) among patients with intracardiac thrombus suggests the presence of an advanced atrial substrate.[4] Contemporary evidence increasingly conceptualizes thromboembolic risk as a property of the atrial myocardium itself—the concept of atrial cardiomyopathy—rather than as a binary consequence of atrial fibrillation. A thrombogenic atrial substrate, characterized by structural, architectural, contractile, and electrophysiological remodeling, can give rise to atrial thromboembolism even in the absence of documented arrhythmia and confers risk in proportion to the degree of remodeling, fibrosis, and arrhythmia burden.[6–8] Part of the observed association between SHR and intracardiac thrombus may therefore reflect more advanced atrial disease. Two aspects of the analysis support this interpretation. First, all patients were in sinus rhythm at admission and underwent 24–72-hour Holter monitoring, and PAF was included in the multivariable model; SHR remained independently associated with intracardiac thrombus after adjustment for PAF.[4] Second, patients with intracardiac thrombus had a larger left atrial anteroposterior diameter than those without thrombus (44.1 vs. 42.6 mm, P = 0.009), a crude marker of atrial remodeling.[9] However, dedicated measures of atrial cardiomyopathy, such as left atrial strain, atrial fibrosis imaging, P-wave indices, natriuretic peptide levels, and quantified atrial fibrillation burden obtained through prolonged rhythm monitoring, were not available. Therefore, residual

confounding related to the atrial substrate cannot be excluded. Prospective studies incorporating these markers will be required to disentangle the respective contributions of metabolic stress and structural atrial remodeling.

Toward an Integrated, Multi-Marker Risk Model

Combining SHR with inflammatory markers may improve risk stratification beyond that achieved with any single parameter. A model integrating a metabolic stress axis (SHR), an inflammatory axis (CRP), and an atrial cardiomyopathy axis (left atrial strain, natriuretic peptide levels, and P-wave abnormalities) is biologically plausible and may more accurately identify patients with occult cardioembolic sources who are most likely to benefit from transesophageal echocardiography. The development of such a model in the present study was limited by its single-center, retrospective design, the modest number of outcome events (64 thrombi), and the fact that the SHR cutoff value was derived from the study cohort without external validation.[4] Adequately powered, prospective, multicenter studies with external validation are needed to determine whether an integrated biomarker panel provides superior predictive performance compared with SHR alone.

In summary, metabolic stress, systemic inflammation, and atrial remodeling represent interrelated yet partially independent contributors to cardioembolic risk. These considerations do not diminish the value of SHR as a simple, inexpensive, and widely available biomarker. Rather, they provide a rationale for prospective, mechanistically informed validation and the eventual integration of SHR into a broader risk-stratification strategy for acute ischemic stroke.

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