Echocardiographic Epicardial Fat Thickness and Neutrophil to Lymphocyte Ratio Are Novel Inflammatory Predictors of Cerebral Ischemic Stroke

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Background: The role of epicardial fat thickness (EFT) in ischemic stroke (IS) has not been previously investigated. The aim of the present study was to evaluate EFT and neutrophil/lymphocyte ratio (NLR) among patients with IS and to examine the relationship between these inflammatory markers and the incidence of IS. *Methods:* The cross-sectional design includes 38 patients with IS and 47 age- and sex-matched healthy controls. Echocardiographic measurement of EFT was conducted according to previously published methods. An automated hematology analyzer was used to generate total and differential leukocyte counts from patient blood samples. *Results:* Mean EFT was 4.86 ± .68 mm in the control group and 5.95 ± 1.14 mm in the IS group. EFT was significantly greater in the IS patients in relation to the control group ($P < .001$). Mean NLR was significantly greater among IS patients in relation to the control group (2.5 ± .6 vs. 1.8 ± .4, $P < .001$). No significant confounding factors were identified in the data set. Spearman's correlation analysis revealed a mild, but highly significant correlation between EFT and NLR (r = .293, $P = .006$). *Conclusions:* This study demonstrates for the first time the association between EFT and cerebral IS. Echocardiographic EFT was significantly correlated with NLR. NLR and echocardiographic EFT represent inexpensive and readily available clinical markers that maybe useful in estimating risk of IS. **Key Words:** Cerebral ischemic stroke—epicardial fat thickness—neutrophil/lymphocyte ratio—inflammation.

Atherosclerotic lesions are an important cause of ischemic stroke (IS) worldwide,[1] accounting for approximately 10% of IS in the United States and as much as 30%-40% of all incidence of IS in Asia. Inflammation is the primary factor in the pathogenesis of atherosclerosis.[2] In particular, increasing evidence implicates inflammatory processes in the development of cerebral IS.[3,4] In addition, several prospective studies demonstrated an association between elevated inflammatory markers and increased risk of first time myocardial infarction (MI) and cerebral ischemia.[5,6] Neutrophil/lymphocyte ratio (NLR), derived directly from the white blood cell count, is an established indicator of systemic inflammation and a predictive marker of prognosis and mortality among stroke patients.[7]

Fat deposition surrounding the internal organs is defined as visceral adiposity. The visceral fat surrounding the heart, epicardial fat, underlies the visceral pericardium and is a potential source of inflammatory cytokines and immune cells. Epicardial fat is a metabolically active tissue and a local source of inflammatory mediators associated with the development of atherosclerosis, metabolic

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Received February 17, 2014; revision received April 11, 2014; accepted April 16, 2014.
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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.04.028

syndrome, and cardiovascular disease.[8,9] Recent studies have demonstrated that epicardial fat thickness (EFT) maybe a valuable indicator of atherosclerosis. Assessment of parameters of subclinical vascular damage, including carotid intima-media thickness, coronary artery calcification, and arterial stiffness, is a routine component of public health screening and may enhance cerebrovascular and cardiovascular disease risk stratification.[8,9] Atherosclerotic processes may occur for years before the emergence of clinical vascular disease; therefore, markers of early atherosclerosis such as EFT are essential for directing preventative care.[8] Previous studies have demonstrated an association between EFT and coronary artery disease, carotid atherosclerosis, metabolic syndrome, and obesity.[8,10] However, the relationship between EFT and IS remains unknown. The aim of the present study is to evaluate EFT and NLR in IS patients and evaluate the relationship of these parameters with cerebrovascular disease.

Materials and Methods

Patients admitted to the Neurology Department of Dicle University Faculty of Medicine Hospital diagnosed with IS, hospitalized, and followed up between May 2012 and May 2013 were enrolled in this study. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee. All participants provided informed consent before enrollment in the study.

The cross-sectional study group included 38 IS patients and 47 age- and sex-matched healthy controls. All participants underwent a complete physical examination, and individual medical histories and clinical features were documented. Body mass index (BMI) was defined as weight (kg) divided by the square of height (m^2). Rankin indexes and the National Institutes of Health Stroke Scale were used to evaluate patient functionality.

Patients were diagnosed with IS using the following methodology: cranial magnetic resonance imaging and computed tomography scans were conducted in all patients. In some patients, repeated magnetic resonance diffusion-weighted imaging confirmed clinical findings consistent with acute infarction.

Biochemical and Hematologic Parameters

All specimens were selected from blood samples within 36 hours from the onset of the disease. An automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, IL) was used to measure total and differential leukocyte counts. Absolute cell counts were used for statistical analysis. Baseline NLR was measured by dividing neutrophil count by lymphocyte count. The Abbott Architect C16000 auto analyzer (Abbott Laboratory) was used to measure total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, thyroid hormones, and glucose levels.

Echocardiography and Epicardial Fat Measurement

All participants underwent transthoracic echocardiography using an echocardiograph equipped with a broadband transducer (Vivid S6, GE Medical Systems, Horten, Norway). Measurements were obtained from the log axis and apical 4-chamber view according to standard criteria. The echocardiographic images were stored in a digital database (EchoPac system, Horten, Norway).

Two cardiologists blinded to the patient information performed the offline EFT measurements. Echocardiographic assessments of the EFT were conducted according to previously published methods. The epicardial fat was identified as the echo-free space between the pericardial layers on the 2-dimensional echocardiography (Fig 1). The maximum EFT was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam perpendicular to the aortic annulus, the anatomic landmark at end systole in 3 cardiac cycles. The interobserver and intraobserver variability of EFT were 2.4% and 1.8%, respectively.

The cause of IS was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[11] Only the patients, diagnosed with large artery atherosclerotic lesions, were included to the study.

The patients and healthy controls with diabetes mellitus (fasting glucose $>$ 126), significant congestive heart failure, atrial fibrillation (AF), dyslipidemia (low-density lipoprotein cholesterol level $>$ 160 mg/dL, triglyceride level $>$ 300 mg/dL), hematologic disease, peripheral artery disease, hypothyroidism, severe renal or liver disease, ongoing infection or systemic inflammation, obesity (BMI $\geq$ 30 kg/m^2), history of hypertension, the use of antihypertensives, and the presence of organ damage were excluded from the study.

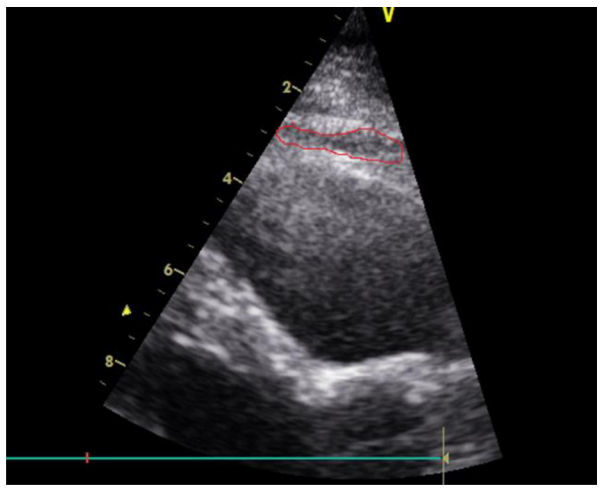

Figure 1. *Epicardial fat thickness (within red shape) is identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium in the parasternal long-axis view.*