JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. ■, NO. ■, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2016.03.006

Association of Soluble CD40 Ligand With Duration of Atrial Fibrillation and With Intensity of Spontaneous Echocardiographic Contrast

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ABSTRACT

OBJECTIVES The authors tested the hypothesis that the inflammatory response of nonvalvular atrial fibrillation (NVAF) is associated with elevated soluble CD40 ligand (sCD40L).

BACKGROUND NVAF is generally believed to be an inflammatory disease process. sCD40L represents a sensitive in vivo indicator of platelet activation and may serve as an "inflammatory and thrombotic thermometer."

METHODS Plasma sCD40L was measured using enzyme-linked immunoadsorbent assay in 109 NVAF cases (60.9 ± 15 years of age; 26% women) and 48 normal sinus rhythm (NSR) controls (62.3 ± 15 years of age; 44% women). Patients were separated by arrhythmia duration of <1 month (n = 21), 1 to 12 months (n = 18), and >12 months (n = 70).

RESULTS Median sCD40L level was significantly higher in NVAF cases than in NSR controls (321 pg/ml vs. 238 pg/ml, respectively; p = 0.029). This difference was driven by higher levels in patients with NVAF duration for <1 month (552 pg/ml) and 1 to 12 months (328 pg/ml). NVAF patients with arrhythmia duration for over 1 year had sCD40L levels not significantly different from those of NSR controls. An sCD40L concentration of 552 pg/ml distinguished NVAF patients with dysrhythmia duration of <1 month (area under the curve [AUC] of 0.72; p = 0.0010) or duration for ≤12 months (AUC: 0.69; p = 0.0003) from NSR controls. Circulating sCD40L levels were also significantly higher among patients with mild spontaneous echocardiogram contrast (SEC) (p = 0.0378) and those with moderate SEC (p = 0.007) compared with NSR controls.

CONCLUSIONS sCD40L levels are significantly higher in NVAF patients than in NSR controls but only for up to 1 year after development of dysrhythmia. An sCD40L concentration of 552 pg/ml can help to assess development or recurrence of asymptomatic NVAF. (J Am Coll Cardiol EP 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

Atrial fibrillation is a common cardiac dysrhythmia associated with an increased risk of cardioembolic stroke in the setting of left atrial appendage thrombosis (LAAT) (1-4). The timing of atrial fibrillation initiation or recurrence is relatively easy if associated with typical symptoms. However, asymptomatic atrial fibrillation is frequent and presents challenges to the clinician with regard to management. Two major clinical scenarios related to this problem are evaluation of cause of cryptogenic stroke and assessment of possible recurrence of atrial fibrillation after original induced or spontaneous reversal to sinus rhythm.

There is growing evidence that provocation, initiation, and progression of atrial fibrillation carries an inflammatory component related directly to the extent of arrhythmia burden (5,6). This is particularly evident with increasing left atrial blood stasis and LAAT formation (7). Whether this inflammatory "expansion" is exclusive to the initial phase of

From the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota. This work was supported by Department of Internal Medicine, Mayo Clinic, grant CR 17896; statistical support was provided by a Mayo Clinic Division of Cardiology internal grant. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 19, 2015; revised manuscript received March 3, 2016, accepted March 10, 2016.

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CD40L = CD40 ligand

CHA2DS2-VASc = congestive heart failure, hypertension, age years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, sex

CHADS2 = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack

CI = confidence interval

LAA = left atrial appendage

LAAT = left atrial appendage thrombus

LVEF = left ventricular ejection fraction

NSR = normal sinus rhythm

NVAF = nonvalvular atrial fibrillation

OR = odds ratio

sCD40L = soluble CD40 ligand

SEC = spontaneous echocardiogram contrast

TEE = transesophageal echocardiogram

arrhythmogenesis or persists thereafter is unknown. It is plausible that the inflammatory component subsides during the scarification phase of endomyocardial and myocardial fibrosis. Conversely, it is likewise possible that variables governing inflammation persist throughout the lifetime of the individual once established.

CD40 ligand (CD40L), a member of the tumor necrosis factor transmembrane protein superfamily, is promptly expressed on the platelet cell surface following activation and thrombus participation (8). CD40L is subsequently cleaved generating soluble CD40 ligand (sCD40L). On the platelet cell surface, sCD40L and CD40L induce endothelial cells to recruit leukocytes and promote thrombin generation through overexpression of tissue factor (9,10). Although 95% of circulating sCD40L comes from platelets, this measurement may represent a sensitive indicator of platelet activation and may serve as an "inflammatory and thrombotic thermometer" for the individual (11,12).

Elevated sCD40L has been found in various diseases and cardiovascular conditions that is associated with atrial fibrillation and has been shown to predict ischemic stroke and other adverse cardiovascular events (13–16). Increased sCD40L is an independent predictor of atrial fibrillation development after coronary artery bypass grafting (17). In those patients with preexisting atrial fibrillation, sCD40L concentrations exceeding 476 pg/ml had a nearly 5-fold higher likelihood of suffering a vascular event (18). However, the relationship between elevated sCD40L and atrial fibrillation was not consistently demonstrated in case-control studies (19–21). It has been concluded that this association is weak at best and is likely explained by common comorbidities seen in this patient population (22). However, in a cohort of paroxysmal atrial fibrillation patients undergoing pulmonary vein isolation, atrial fibrillation induced by catheter stimulation in the electrophysiology laboratory resulted in rapid and significant rise of sCD40L levels (23). This contradiction may reflect a transitory nature of sCD40L elevation, which may be very time-dependent relative to the trigger or onset of this dysrhythmia.

We therefore sought to test the hypothesis that sCD40L is augmented only during the initial onset of nonvalvular atrial fibrillation (NVAF) and is governed by the degree of left atrial blood stagnation. To test this hypothesis, we compared plasma sCD40L concentrations in patients with different atrial fibrillation durations and in normal sinus rhythm (NSR) controls.

MATERIALS AND METHODS

PATIENT RECRUITMENT. Study design, patient selection, recruitment, and clinical and echocardiographic data collection and assessment have been described previously (7). Briefly, all patients with NVAF (cases) who had transesophageal echocardiogram (TEE) ordered by their primary physician or cardiologist (from October 4, 2007, to April 27, 2009) were approached for study participation, unless they had: 1) acute illness, stroke, myocardial infarction, or surgery within 30 days; 2) more than moderate heart valve disease; 3) artificial heart valves; 4) previously unprovoked venous or arterial thrombosis; 5) prior major bleeding unrelated to warfarin therapy; 6) liver disease; 7) active malignancy; or 8) hormonal stimulation (estrogen/progesterone therapy or pregnancy). Control subjects in NSR with no history of atrial fibrillation were recruited from the Primary Care Internal Medicine clinic during their annual medical examination. From our original cohort (7), a subgroup of subjects who were not on antiplatelet therapy was randomly sampled for analysis of this study. The details of the screening process and patient recruitment are provided in the Online material.

TRANSESOPHAGEAL ECHOCARDIOGRAM. TEE was performed as previously described (24,25). LAAT was defined as an echogenic mass in the appendage or body of the atrium, distinct from the underlying endocardium and pectinate muscles and detected in more than 1 imaging plane (24,25). Spontaneous echocardiogram contrast (SEC) was defined as a pattern of dynamic "smoke-like," slowly swirling, intracavitary echo densities imaged with gain settings adjusted to eliminate background noise. SEC was graded as "absent" (Fatkin criterion: 0), "mild" (Fatkin criteria: 1 and 2), "moderate" (Fatkin criterion: 3), or "severe" (Fatkin criterion: 4), according to the published echocardiographic criteria by Fatkin et al. (26) with modification. Left atrial appendage emptying velocity profiles were measured over 5 consecutive cardiac cycles, with the sample volume positioned 1 cm within the orifice of the left atrial appendage (LAA) (27). The left ventricular ejection fraction (LVEF) was visually estimated. Aortic atherosclerosis severity was defined as "simple" when atheroma thickness was <4 mm and immobile when "severe" when atheroma exceeded 4 mm or contained mobile components (27). Left atrium