ORIGINAL ARTICLE

Markers of coagulation and fibrinolysis do not detect or predict the presence of left atrial appendage thrombus in patients with atrial fibrillation

Atriyal fibrilasyonu olan hastalarda pıhtılaşma ve fibrinolizis belirteçleri sol atriyal trombüs varlığını belirleyemiyor veya öngöremiyor

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ABSTRACT

Objective: This study was designed to evaluate the role of hemostatic variables in arterial blood serum in left atrial thrombosis and to define any hemostatic variables, such as serum biomarkers, that could potentially reduce the need for transesophageal echocardiography.

Methods: This study included patients with non-valvular asymptomatic atrial fibrillation (AF), either paroxysmal, persistent, or chronic. The presence of an left atrial appendix (LAA) thrombus was used to form 2 groups: thrombus (+) and thrombus (-). The serum levels of the thrombotic/fibrinolytic markers including beta-thromboglobulin, prothrombin fragment 1+2, thrombin/antithrombin complex, human plasminogen activator inhibitor-1/tissue plasminogen activator complex, and D-dimer were compared between 2 groups.

Results: The mean age of the study population was 65.6±12.2 years (range: 30–96 years), and 33 (61.1%) patients were male. Fourteen (25.9%) patients had an LAA thrombus and 40 patients did not. Two groups did not differ significantly with regard to any of the coagulation/fibrinolysis markers. The LAA thrombus (+) group had significantly higher rates of heart failure, peripheral artery disease, coronary artery disease, and chronic obstructive pulmonary disease ($p<0.05$). Neither the serum levels of the study markers nor demographic and clinical parameters were predictive of an LAA thrombus in binary logistic regression analysis.

Conclusion: The arterial blood serum markers did not differ significantly between groups with and without an LAA thrombus and did not predict an LAA thrombus in patients presenting with AF.

ÖZET

Amaç: Sol atriyal trombozis varlığında arter kan serumundaki hemostatik değişkenlerin rolünü değerlendirmek. Serum biyobelirteçleri gibi transözofageal ekokardiyografi ihtiyacını potansiyel olarak azaltabilecek olan hemostatik değişkenleri tanımlamak.

Yöntemler: Bu çalışmaya non-valvüler asemptomatik atriyal fibrilasyonlu (AF); paroksismal, persistent veya kronik, hastalar alındı. Hastalar sol atriyal apendiks (SAA) trombüsünün varlığına göre, SAA trombüsü olanlar (Grup 1) ve SAA trombüsü olmayanlar (Grup 2) olmak üzere iki gruba ayırıldı. Bu iki grup arasında serum trombotik/fibrinolitik belirteçlerinin (beta-tromboglobulin, protrombin fragmanı 1 + 2, trombin/antitrombin kompleksi, insan PAI-1/tPA kompleksi ve D-dimer) düzeyleri arasındaki fark karşılaştırıldı.

Bulgular: Çalışma popülasyonunun yaş ortalaması 65.6±12.2 yıldı (dağılım 30–96 yaş) ve 33'ü (%61.1) erkekti. On dört (%25.9) hastada SAA trombüsü vardı, 40 hastada yoktu. İki gruptada pıhtılaşma / fibrinoliz belirteçlerinin herhangi birine göre anlamlı bir farklılık göstermedi. SAA trombüs (+) grubu, kalp yetmezliği, periferik arter hastalığı, koroner arter hastalığı ve kronik obstrüktif akciğer hastalığı oranlarında anlamlı olarak daha yüksek oranlara sahipti ($p<0.05$). Çalışmada değerlendirilen hemostatik değişkenlerin serum seviyeleri ve demografik ve klinik parametreler, ikili lojistik regresyon analizinde SAA trombüsünü belirleme konusunda anlamlı bulunmadı.

Sonuç: Arteriyel kan serumu belirteçleri, SAA trombüsü olan ve olmayan gruplar arasında farklılık göstermedi. AF ile gelen hastalarda SAA trombüsünü göstermede istatistiki olarak anlamsız bulundu.

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Atrial fibrillation (AF) is the most common sustained rhythm disorder worldwide.[1] The thrombotic state associated with AF is responsible for a large proportion of stroke and systemic thromboembolism cases.[2,3] The suggested mechanism for thrombus formation in AF is traditionally based on Virchow's triad, which states that atrial endocardial damage, blood stasis, and a hypercoagulable state are responsible for thrombus formation.[4,5]

Abbreviations:

AF	*Atrial fibrillation*
β-TG	*Beta-thromboglobulin*
DD	*D-dimer*
ELISA	*Enzyme-linked immunosorbent assay*
LAA	*Left atrial appendage*
MRI	*Magnetic resonance imaging*
PAI-1	*Plasminogen activator inhibitor type 1*
PTF1-2	*Prothrombin fragment 1+2*
TAT	*Thrombin-antithrombin*
TEE	*Transesophageal echocardiography*
TPA	*Tissue plasminogen activator*

Traditionally, patients with AF of unknown duration or exceeding 48 hours are considered at increased risk of left atrial thrombus formation, most of which tend to occur in the left atrial appendage (LAA), with a risk of thromboembolism. Currently, transesophageal echocardiography (TEE) is the gold standard method to detect intracardiac thrombus.[6] However, this semi-invasive procedure can have rare, but potentially catastrophic, complications, such as pulmonary aspiration, hypoxia, hypotension, laryngeal or vocal cord injury, laryngospasm, or esophageal rupture.[7,8] Furthermore, the requirement that patients fast for at least 4–6 hours prior; the side effects of sedatives, including respiratory depression and prolonged sedation; the need for a team to perform and experienced echocardiographers to interpret the procedure; the relatively long preparatory and procedure times; and its prohibitive cost sometimes make the TEE procedure difficult to perform. Therefore, non-invasive markers of left atrial thrombus that could potentially reduce the need for TEE, such as serum biomarkers, would be most welcomed in clinical practice. Although it has been reported that some coagulation markers are released into the circulation during thrombus formation in the left atrium,[9] no serum marker has yet been investigated as a surrogate marker of the presence of left atrial thrombus. The objective of this study was to examine the role of various markers of thrombotic and thrombolytic pathways, namely beta-thromboglobulin (β-TG), prothrombin fragment 1+2 (PTF1+2), thrombin-antithrombin (TAT) complexes, tissue plasminogen activator/plasminogen activator inhibitor (tPA-PAI-1), and D-dimer (DD), in an effort to predict intra-atrial thrombus formation in patients with AF. This research will add to the available knowledge on the clinical question of whether dependence on TEE to rule out left atrial thrombus can be minimized in AF management.

METHODS

Study population

The local ethics committee at Baskent University approved this study, and each participant provided written, informed consent. This study was approved by Baskent University Institutional Review Board and Ethics Committee (Project no: KA14/287) and supported by Baskent University Research Fund. A total of 54 patients older than 18 years who were admitted to the Baskent University Cardiology Department between April 2014 and June 2016 were enrolled. All of the patients had newly diagnosed, non-valvular, asymptomatic AF; therefore, no distinction was made between patients based on duration of the AF episode, i.e., paroxysmal, persistent, or chronic. The following patients were excluded from the study: those who declined to participate in the study or to undergo TEE; those with severe hematological, hepatic, renal, or infectious diseases with an inherently elevated international normalized ratio (≥2.0), a low thrombocyte count (<50,000/mm^3), other severe bleeding diathesis, or signs and symptoms of disseminated intravascular coagulation; those with valvular AF, particularly with mitral stenosis of rheumatic origin and prosthetic heart valves; those using a concurrent or recent parenteral (low-molecular-weight heparins, unfractionated heparin, bivalirudin, huridin, or fondaparinux) (within 24 hours) or oral anticoagulants (coumarin derivatives, novel oral anticoagulants, including dabigatran, apixaban, rivaroxaban, or edoxaban) (within 1 week); those with a history of cardiac surgery or percutaneous intervention with LAA closure; and those with any thrombus outside the left atrium.

The presence of an LAA thrombus was used to form 2 groups: thrombus (+) and thrombus (-). The groups were compared with respect to the serum level of thrombotic/fibrinolytic markers and demographic, echocardiographic, and biochemical variables.

Echocardiographic evaluation

All of the patients underwent echocardiography performed by experienced cardiologists who were blind

to the results of other study tests. All of the echocardiographic examinations were performed with a Vivid E9 digital ultrasound device (GE Healthcare, Inc. Chicago, IL, USA). All of the patients first underwent a comprehensive transthoracic echocardiography examination to determine left ventricular diameter, volume, ejection fraction, left atrial size, and diastolic function. This was followed by TEE, performed after appropriate patient preparation and sedation, to detect a thrombus in the LAA. An LAA thrombus was defined as a mobile, irregularly shaped, greyish, echodense, intracavitary mass with a textured density and which was acoustically distinct from the endocardium and lining of the atrial appendage.

Blood sampling and biomarker assays

All of the blood samples were taken from the right or left radial artery to ensure arterial sampling and remove the possibility of presystemic elimination and distribution of the studied markers. Before centrifugation, the blood samples were allowed to coagulate at room temperature for 20 minutes. After the samples were centrifuged at 4000 rpm, they were kept at -80°C until the day of biochemical analysis. Hemolyzed sera were not studied. The following enzyme-linked immunosorbent assay (ELISA) kits (Cloud-Clone Corp., Katy, TX, USA) were used: Human Beta-Thromboglobulin ELISA kit (Ref: SEA370Hu, Lot: 160106227), Human Prothrombin Fragment 1+2 ELISA kit (Ref: SEA710Hu, Lot: 160203178), Human Thrombin/Antithrombin Complex ELISA kit (Ref: SEA831Hu, Lot: 160203185), Human PAI-1/tPA Complex ELISA kit (Ref: EP1105-1, Lot: 03511508) and Quantia D-dimer ELISA kit (Ref: 7K02-01, Lot: 03016D000) to study the biochemical markers.

In brief, human β-TG is a protein that is stored in alpha-granules of platelets and released in large quantities upon platelet activation. The level is an index of platelet activation.[10]

Human PTF1+2 is an amino-terminal activation product with a molecular weight of 35.5 kDa produced by the conversion of prothrombin to thrombin by activated factor X.[11] PTF1+2 is an indicator of circulating thrombin and thrombotic tendency.

The TAT complex is induced by thrombin and reflects the latent activator of the clotting pathway.[12] Earlier studies have indicated that this parameter may be a sensitive marker for venous thromboembolism of the lower extremities.[13,14]

The t-PA-PAI-1 complex is formed by tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type-1 (PAI-1). Plasmin is the main fibrinolytic component in blood, and its generation is primarily regulated by t-PA, which favors plasmin formation from plasminogen and thus fibrinolysis, and its counterpart (PAI-1), a serine protease synthesized by thrombocytes and endothelium, which blocks the conversion of plasminogen to plasmin and fibrinolysis.[15,16] The plasma concentration of the t-PA/PAI-1 complex reflects those of the 2 assembly proteins and is thus an indicator of the thrombosis-fibrinolysis cycle.

DD is formed as a result of the plasmin degradation of fibrin. It is indicative of an active thrombotic process and a parallel fibrinolytic process, such as venous thromboembolism, cancer, inflammation, or surgery. It is commonly used as a screening tool to exclude deep venous thrombosis and pulmonary thromboembolism in clinical practice.[17]

Statistical analysis

The study data were analyzed using the PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA) software package. The Kolmogorov-Smirnov test was used to test the normality of the distribution of the quantitative data. Normally distributed quantitative variables were reported as mean±SD, non-normally distributed data were reported as median (minimum-maximum), and categorical data as number (n) and percentage (%). The Mann-Whitney U test was used to compare non-normally distributed quantitative variables between the study groups. The Student's t-test was used to compare normally distributed quantitative data, and Pearson's chi-square/Fisher's exact tests were used to compare categorical variables between the study groups. A binary logistic regression analysis was used to determine the significant predictors of LAA thrombus. All of the results were reported with a confidence interval of 95% and at a significance level of $p<0.05$.

RESULTS

The mean age of the study population was 65.6±12.2 years (range 30-96 years), and 33 (61.1%) patients were male. The 2 groups had a similar median age. Fourteen (25.9%) patients had an LAA thrombus and

40 patients did not. The males had a significantly higher rate of LAA thrombus presence (n=12, 36.4%) than the females (n=2, 9.5%) (p<0.05). The LAA thrombus (+) group had significantly higher rates of heart failure, peripheral artery disease, coronary artery disease and chronic obstructive pulmonary disease (p<0.05), but the other demographic properties were comparable between the groups, as well as the $CHADS_2$ and the CHA_2DS_2-VASc scores (Table 1). The 2 groups did not differ significantly regarding any of the coagulation/

Table 1. Comparison of the demographic properties of the LAA thrombus (+) and (–) groups

Variable	LAA thrombus (+) group (n=14)	LAA thrombus (–) group (n=40)	*p*
Age (years)	67 (44–75)	68.5 (30–96)	NS
Sex (male), n (%)	12 (85.7)	21 (52.5)	<0.05*
Hypertension, n (%)	8 (57.1)	26 (65)	NS
Diabetes mellitus, n (%)	7 (50)	9 (22.5)	NS
Coronary artery disease/peripheral arterial disease, n (%)	10 (71.4)	15 (37.5)	<0.05**
Heart failure, n (%)	8 (57.1)	9 (22.5)	<0.05**
Cerebrovascular accident, n (%)	1(7.1)	1 (2.5)	NS
Hyperlipidemia, n (%)	6 (42.9)	14 (35)	NS
Chronic obstructive pulmonary disease, n (%)	8 (57.1)	3 (7.5)	<0.05**
Malignancy, n (%)	0 (0)	4 (10)	NS
Thyroid disease, n (%)	0 (0)	4 (10)	NS
Smoking, n (%)	6 (42.9)	9 (22.5)	NS
Use of aspirin, n (%)	8 (57.1)	12 (30)	NS
Use of clopidogrel, n (%)	5 (35.7)	2 (5.0)	NS
Use of dual antiplatelet agents, n (%)	4 (28.6)	3 (7.5)	NS
$CHADS_2$ score	2.5 (0–4)	2 (0–5)	NS
CHA_2DS_2-VASc score	3.5 (0–6)	3 (0–8)	NS

*Mann-Whitney U test; **Fisher's exact test. LAA: Left atrial appendage.

Table 2. Comparison of the study parameters and blood count parameters between the LAA thrombus (+) and (–) groups

Parameter	LAA thrombus (+) group	LAA thrombus (–) group	*p**
D-dimer	0.34 (0.20–2.20)	0.30 (0.14–0.85)	NS
tPA-PAI-1 complex	14.76 (2.76–16.72)	14.40 (5.20–17.68)	NS
Beta-thromboglobulin	10702.00 (4375.00–23507.00)	10359.50 (625.00–29166.50)	NS
Thrombin-antithrombin complex	92425.00 (30200.00–519450.00)	87700.00 (22100.00–488900.00)	NS
Human prothrombin fragment 1+2	11870.00 (1580.00–74220.00)	14900.00 (2580.00–532000.00)	NS
CRP (mg/dL)	2.29 (0–25)	2.23 (0–29)	NS
Platelet count ($10^3/\mu L$)	187 (161–245)	254 (130–523)	NS
Neutrophil count ($10^3/\mu L$)	61 (46.7–82.8)	59.4 (41.3–84.3)	NS
Lymphocyte count ($10^3/\mu L$)	27 (13.3–41.4)	29.5 (10.1–48.3)	NS
RDW (%)	13.9 (11.2–16.1)	14.1 (10.8–19.7)	NS
MCV (fL)	89.7 (82.3–94.0)	86.1 (8.6–95.3)	NS
MPV (fL)	8.7 (5.5–12.3)	8.6 (5.9–12.9)	NS

*Mann-Whitney U test. CRP: C-reactive protein; LAA: Left atrial appendage; MCV: Mean corpuscular volume; MPV: Mean platelet volume; RDW: Red cell distribution width; TPA-PAI-1: Tissue plasminogen inhibitor/plasminogen activator inhibitor type 1.

fibrinolysis markers (Table 2). In logistic regression analysis, neither an LAA thrombus nor spontaneous echo contrast could be independently predicted by any of the coagulation/fibrinolysis markers, blood count parameters, or demographic variables.

DISCUSSION

Our study's main finding is the inability of various coagulation/fibrinolysis markers to distinguish patients with AF and LAA thrombus from those with AF but no LAA thrombus. It has been consistently shown that patients with AF are at increased risk of thromboembolic complications, due to thrombi most commonly originating from the LAA.[18] However, mechanisms underlying thrombus formation in AF are not clearly understood, although Virchow's triad traditionally dictates that vascular wall damage, blood stasis, and a hypercoagulable state are responsible for thrombus formation in the cardiovascular system.[4,5,19,20] We compared the hypercoagulable state component of Virchow's triad between AF patients with and without LAA thrombus by studying the levels of several coagulation/fibrinolysis markers in an effort to identify 1 or more surrogate biomarkers of LAA thrombus. However, we failed to detect any significant difference between the DD, PTF 1+2, TAT, and β-TG levels of AF patients with and without LAA thrombus. This finding may have several explanations. First, the coagulation and fibrinolytic systems may be universally activated in AF, regardless of the presence of LAA thrombus. Consistent with this hypothesis, previous randomized studies[20–25] and a meta-analysis of 59 studies[26] reported increased levels of coagulation/fibrinolytic system components, including β-TG, DD, TAT, and PTF 1+2, in patients with AF compared with controls. Since not all patients with AF have an LAA thrombus, thrombus formation in an LAA may require additional factors, which may not be uniformly distributed across the general AF population, including endothelial dysfunction,[27] reduced ejection fraction,[28] atrial dilatation,[29] systemic inflammation,[30] prothrombotic state,[5] and blood stasis.[31] Universal activation of the coagulation and fibrinolysis cascades in AF may be mediated by inflammation and endothelial dysfunction.[32] In accordance with this hypothesis, our AF patients with an LAA thrombus had a significantly higher prevalence of atherosclerosis and chronic obstructive pulmonary disease, 2 conditions characterized by systemic inflammation and a prothrombotic state.[33–35] The second possibility is that some of our patients may have had old, more stable thrombi, and the levels of some coagulation and/or fibrinolysis markers may have normalized. Although poorly studied in AF, several studies of deep vein thrombosis have indicated that at least some coagulation markers return quickly to baseline after formation of a deep venous thrombus.[36,37] Since our study did not provide definitive information as to the age of an LAA thrombus, we could not confirm the old thrombus hypothesis because we did not employ certain modalities that could distinguish fresh vs old thrombi, such as echocardiography[38] and cardiac magnetic resonance imaging (MRI).[39,40] Third, we may have inadvertently categorized some, if not all, patients who had microemboli too small to be visualized by TEE as thrombus (-). This, in turn, might have reduced the difference in the levels of the studied markers between the 2 groups, explaining the lack of statistical significance of inter-group differences. This possibility has been suggested in the literature. Sugioka et al.[41] reported a low prevalence of left atrial thrombus (1.9%) among patients with AF and silent brain infarcts on brain MRI and suggested microembolism as the culprit for the silent brain infarcts. Similarly, Gaita et al.[42] and Feinberg et al.[43] found microemboli not visualized by conventional echocardiographic techniques to be the predominant cause of silent cerebral embolism episodes. Consistent with this hypothesis, our study failed to demonstrate any significant correlation between an LAA thrombus and the CHA_2DS_2-VASc or $CHADS_2$ scores, which are well-known risk scores for stroke, raising the possibility that we may have been compelled to categorize some, if not all, patients with microemboli not visualizable by TEE as thrombus (-), which may have precluded a statistically significant difference between the thrombus (+) and (-) groups. Therefore, an LAA thrombus screening strategy based solely on TEE may be too simplistic and inadequate to detect LAA thrombi, and additional advanced techniques or biochemical markers to detect microthrombi may be necessary. Finally, we offer that the TEE procedure in our study may have missed LAA thrombi that had previously been present but were lysed or embolized at the time of the procedure due to the dynamic nature of LAA thrombi. Since this was a cross-sectional study, we could not follow the life span of LAA thrombi in our patients. We suggest that this represents another topic of research.

Limitations

First, as we did not enroll healthy controls without AF, we could not determine the levels of coagulation/fibrinolysis markers in healthy subjects and compare them with those of AF patients; therefore, we failed to confirm a universal increase of these levels in AF patients. Second, we were unaware of the age of the LAA thrombi and therefore could not make any interpretation about the role of the age of the thrombus on the level of these markers. Future studies that compare coagulation/fibrinolysis markers between patients with old vs fresh thrombi distinguished by specialized imaging techniques may shed light on this subject. Lastly, we sampled only some coagulation/fibrinolysis system components as the study markers and cannot offer any interpretation regarding other components of either system.

Conclusion

In conclusion, the serum DD, TAT, tPA/PAI-I, β-TG, and PTF1+2 levels did not differ between groups with and without an LAA thrombus and were not predictive of LAA thrombus in patients presenting with AF. Additional research that compares AF patients with fresh and old thrombi with respect to the blood levels of coagulation/fibrinolytic markers may provide useful information on their ability to distinguish fresh vs old thrombi.

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