ORIGINAL ARTICLE

Thromboembolic events are associated with prolonged clot lysis time in patients with permanent atrial fibrillation

Michał Ząbczyk[1], Jacek Majewski[2], Jacek Lelakowski[2]

1 Department of Cardiac Surgery, Anesthesiology and Experimental Cardiology, Institute of Cardiology, Jagiellonian University, Medical College, John Paul II Hospital, Kraków, Poland
2 Department of Electrocardiology, Institute of Cardiology, Jagiellonian University, Medical College, John Paul II Hospital, Kraków, Poland

KEY WORDS

atrial fibrillation, clot lysis time, fibrinolysis, stroke, thromboembolism

ABSTRACT

INTRODUCTION Atrial fibrillation (AF) is associated with a prothrombotic state.

OBJECTIVES We evaluated associations of previous thromboembolic events with fibrinolytic parameters in patients with AF.

PATIENTS AND METHODS We studied 62 consecutive patients with permanent AF (27 men, 35 women, aged 46–89 years [median, 78 years]). Patients receiving warfarin or acenocoumarol on a long-term basis were eligible. We determined plasma fibrin clot lysis time (CLT), plasminogen activator inhibitor-1 (PAI-1) antigen, thrombin-activatable fibrinolysis inhibitor (TAFI) activity and antigen, plasminogen, α_2-antiplasmin (α_2AP), and soluble thrombomodulin (sTM).

RESULTS There were 19 subjects (30.6%) with a history of thrombotic events (stroke in 11, myocardial infarction in 8, and pulmonary embolism in 3 patients). They had longer CLT ($P = 0.0035$ for patients with previous stroke and $P = 0.001$ for patients with any previous thrombotic event), together with higher PAI-1 ($P = 0.025$ and $P = 0.016$, respectively), TAFI activity ($P = 0.002$ and $P = 0.011$, respectively), sTM ($P = 0.0023$ and $P = 0.012$, respectively), and α_2AP ($P = 0.007$ and $P = 0.0006$, respectively) than the remaining subjects. AF patients with previous stroke had also higher TAFI antigen than the remainder ($P = 0.04$). CLT ($P = 0.024$), PAI-1 ($P = 0.022$), TAFI activity ($P = 0.048$), and sTM ($P = 0.032$, all P for trend) increased with higher CHA_2DS_2-VASc scores. CLT was not associated with time from thrombotic event to enrollment. Patients taking oral anticoagulants (n = 46) had only slightly higher sTM levels (3.6 [2.9–6.3] vs. 2.9 [2.2–4.1] ng/ml, $P = 0.049$) than the remaining subjects.

CONCLUSIONS Stroke or other thromboembolic event in AF patients is associated with impaired lysability of fibrin clots combined with elevated PAI-1, TAFI, sTM, and α_2AP.

Correspondence to:
Michał Ząbczyk, MSc, Instytut Kardiologii, Uniwersytet Jagielloński, Collegium Medicum, ul. Prądnicka 80, 31-202 Kraków, Poland,
phone: +48-12-614-31-43,
fax: +48-12-614-31-43,
e-mail: michalzabczyk@op.pl
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INTRODUCTION Atrial fibrillation (AF) is the most common cardiac arrhythmia. AF is associated with a prothrombotic state reflected by elevated thrombin generation markers, including F1 + 2 prothrombin fragments, or D-dimer.[1,2] It has also been shown that increased levels of plasminogen activator inhibitor 1 (PAI-1) occur in patients with AF.[3] Other hypercoagulability markers detected in permanent AF involved increased levels of plasma fibrinogen, von Willebrand factor, and soluble P-selectin.[4] It is well known that AF is associated with an increased risk of stroke and arterial thromboembolism, which can be effectively reduced by anticoagulation.[5,6] In AF patients aged 75 years or older taking adjusted-dose of warfarin, the stroke rate per year was nearly half lower compared with AF patients on aspirin.[7] AF is also associated with an increased risk of myocardial infarction (MI).[8] Moreover, vascular endothelial cell damage is observed in AF patients as evidenced by elevated soluble thrombomodulin (sTM).[9] TM, an integral

membrane protein expressed on the surface of endothelial cells, binds thrombin with high affinity.[10] The TM-thrombin complex also inhibits fibrinolysis by cleaving thrombin-activatable fibrinolysis inhibitor (TAFI) into its active form.[10] It has been shown that in patients with AF who experienced an acute cardiovascular or cerebrovascular event, sTM levels were significantly increased compared with AF patients without a history of such events.[8] Formation of fibrin clots relatively resistant to lysis represents the final step in blood coagulation. Fibrin clot formation and degradation are largely determined by plasma fibrinolytic potential. Fibrin is degraded primarily by plasmin which circulates as a zymogen, plasminogen.[11] However, fibrinolysis in the general population appears to be controlled predominantly by α_2-antiplasmin (α_2AP), PAI-1, and TAFI.[11] α_2AP is the primary physiological inhibitor of plasmin.[11] Elevated α_2AP levels are independently associated with the risk of MI.[12]

PAI-1 is a direct inhibitor of the plasminogen activation system but its interaction with the adhesive glycoprotein vitronectin plays a role in tissue remodeling and metastasis.[13] High PAI-1 levels have been associated with an increased risk of coronary artery disease (CAD) and MI, probably resulting from inhibition of fibrinolysis.[13]

Plasma TAFI levels are associated with the risk of deep vein thrombosis and ischemic stroke.[14,15] Elevated TAFI concentrations and enhanced thrombin generation in hypertensive patients may contribute to atherosclerosis progression in this population.[16]

Clot lysis time (CLT) represents an overall plasma fibrinolytic capacity. In the general population, the main determinants of CLT are PAI-1 levels followed by plasminogen, TAFI, prothrombin, a^{oo}nd α_2AP.[17] Hypofibrinolysis reflected by CLT in patients with venous thrombosis is predominantly associated with elevated plasma levels of TAFI and PAI-1.[17] Decreased fibrinolytic potential expressed as prolonged CLT has been reported in patients with idiopathic venous thromboembolism, peripheral arterial disease, acute coronary syndrome, or ischemic stroke.[18-21] Hypofibrinolysis increases also the risk of the first MI in young men.[22] Current evidence indicates that CLT could be a marker of both venous and arterial thromboembolism. To our knowledge, CLT has not been investigated in AF patients.

The aim of the current study was to investigate CLT and its determinants with regard to thromboembolic events in patients with AF. We hypothesized that a history of thromboembolic events is linked with impaired fibrinolysis reflected by prolonged CLT in AF patients at least in part due to altered plasma pattern of PAI-1, TAFI, or α_2AP.

PATIENTS AND METHODS

Patients We enrolled 62 consecutive patients with permanent nonvalvular AF of 6-month duration or longer. All eligible patients had electrocardiographically confirmed long-term AF. The exclusion criteria were as follows: any acute illness, known cancer, hepatic or renal dysfunction, heart failure (New York Heart Association III or IV), idiopathic cardiomyopathy, recent thromboembolic event (<3 months), autoimmune disease, and steroid administration. Patients receiving warfarin or acenocoumarol on a long-term basis were eligible if their anticoagulation was stable within the previous 3 months.

Data on demographics, cardiovascular risk factors, and current treatment were collected from all patients using a standardized questionnaire. Diabetes was defined as a history of diabetes regardless of duration of the disease, a need for hypoglycemic agents, or fasting glycemia greater than 7 mmol/l or 126 mg/dl. CAD was confirmed angiographically (>50% stenosis in at least 1 major epicardial artery). The diagnosis of stroke was based on the World Health Orgnization criteria. Pulmonary embolism (PE) was diagnosed based on clinical presentation and documented by computed tomography scanning.

The CHA_2DS_2-VASc (Congestive heart failure/left ventricle dysfunction, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack/thromboembolism, Vascular disease, Age 65–74 years, Sex category) score was used to assess the risk for stroke and thromboembolism in AF patients.[23]

The University Ethical Committee approved the study and patients provided written informed consent.

Methods **Laboratory tests** Fasting blood samples were drawn between 8 a.m. and 10 a.m. from an antecubital vein with minimal stasis. Creatinine, glucose, and international normalized ratio (INR) were assessed by standard automated laboratory methods. Plasma samples (9:1 of 3.2% trisodium citrate) for the analysis of fibrinolysis were centrifuged (20 min, 2500 g) within 30 minutes of collection, immediately frozen, and stored in aliquots at –80°C. Fibrinogen and C-reactive protein (CRP) were measured by latex nephelometry (Dade Behring, Marburg, Germany). D-dimer was determined by an enzyme-linked immunosorbent assay (ELISA; American Diagnostica, Stanford, Connecticut, United States). Plasma α_2AP and plasminogen were measured by chromogenic assays (STA-Stachrom antiplasmin and STA-Stachrom plasminogen, Diagnostica Stago, Asniéres, France). Normal values in elderly patients (n = 30) for α_2AP were 82%–142% and for plasminogen 75%–144%. Plasma PAI-1 antigen levels were measured by an ELISA (American Diagnostica). Normal values for PAI-1 were 4–34 ng/ml. Measurement of TAFI antigen was performed with an ELISA (Chromogenix, Lexington, Massachusetts, United States). Normal values for TAFI antigen were 79%–147%. Plasma TAFI activity was measured by a chromogenic assay using the ACTICHROME® Plasma TAFI Activity Kit (American Diagnostica). Normal values for TAFI activity were 17–40 µg/ml. sTM was measured by an ELISA (Diagnostica Stago, Asniéres, France). Normal

TABLE Characteristics of patients with atrial fibrillation

Variable	All patients (n = 62)	Patients with previous stroke (n = 11)	Patients without previous stroke (n = 51)	*P*	Patients with previous thrombotic event (n = 19)	Patients without previous thrombotic event (n = 43)	*P*
age, y	78 (73–82)	78 (70–81)	78 (73–83)	0.64	78 (74–81)	78 (73–83)	0.89
male sex, n (%)	27 (43.5)	6 (54.5)	21 (41.2)	0.42	10 (52.6)	17 (39.5)	0.34
BMI, kg/m^2	27 (24–28)	24 (24–29)	27 (24–28)	0.63	26 (24–28)	27 (24–28)	0.73
hypertension, n (%)	28 (45.2)	8 (72.7)	20 (39.2)	0.09	12 (63.2)	16 (37.2)	0.06
current smoking, n (%)	1 (1.6)	1 (9.1)	0	0.39	1 (5.3)	0	0.67
diabetes mellitus, n (%)	17 (27.4)	5 (45.5)	12 (23.5)	0.14	7 (36.8)	10 (23.3)	0.27
coronary artery disease, n (%)	9 (14.5)	2 (18.2)	7 (13.7)	0.93	6 (31.6)	3 (7.0)	0.032
valve surgery, n (%)	9 (14.5)	2 (18.2)	7 (13.7)	0.93	3 (15.8)	6 (14.0)	0.84
time from thromboembolic event, mo	105.7 ±74.0	101.4 ±63.8	112.4 ±93.0	0.77	105.7 ±74.0	0	–
echocardiography							
left atrium[a], mm	54.0 ±7.1	54.0 ±7.7	54.0 ±7.1	0.99	51.4 ±6.8	55.1 ±7.0	0.14
medication							
vitamin K antagonists, n (%)	46 (74.2)	9 (81.8)	37 (72.5)	0.80	16 (84.2)	30 (69.8)	0.38
aspirin, n (%)	15 (24.2)	2 (18.2)	13 (25.5)	0.90	5 (26.3)	10 (23.3)	0.80
statins, n (%)	29 (46.8)	8 (72.7)	21 (41.2)	0.12	13 (68.4)	16 (37.2)	0.024
ACEIs, n (%)	27 (43.5)	6 (54.5)	21 (41.2)	0.42	10 (52.6)	17 (39.5)	0.34
β-blockers, n (%)	30 (48.4)	4 (36.4)	26 (51.0)	0.58	9 (47.4)	21 (48.8)	0.92
laboratory variables							
fibrinogen, g/l	3.4 (2.9–3.7)	3.4 (2.7–3.8)	3.4 (2.9–3.7)	0.63	3.4 (3.1–3.7)	3.4 (2.8–3.8)	0.74
C-reactive protein, mg/l	1.9 (1.0–4.5)	2.5 (1.1–3.2)	1.8 (1.0–4.9)	0.45	2.5 (1.2–4.9)	1.8 (1.0–5.3)	0.15
D-dimer, µg/l	230.5 (190.0–408.0)	210 (172–440)	234 (195–408)	0.21	230 (177–445)	234 (195–406)	0.74
sTM, ng/ml	3.3 (2.8–5.4)	7.6 (5.4–8.9)	3.1 (2.8–4.1)	0.0023	6.7 (2.9–7.9)	3.0 (2.7–4.1)	0.012
CLT, min	98.4 ±17.7	112.2 ±16.4	95.4 ±16.6	0.0035	109.2 ±15.6	94.2 ±16.3	0.001
PAI-1 antigen, ng/ml	21.0 (17.9–30.7)	28.3 (22.0–34.7)	20.3 (17.2–29.4)	0.025	27.1 (20.5–33.7)	19.9 (17.2–29.4)	0.016
TAFI activity, µg/ml	30.3 ±7.4	36.4 ±6.8	28.9 ±6.9	0.002	33.8 ±8.3	28.8 ±6.4	0.011
TAFI antigen, %	108.7 ±14.6	116.8 ±13.4	106.9 ±14.3	0.04	111.6 ±15.6	106.9 ±14.2	0.30
plasminogen, %	102.4 ±12.2	98.3 ±12.2	103.3 ±12.1	0.22	99.2 ±13.2	103.9 ±11.7	0.18
α_2AP, %	103.9 ±11.9	112.5 ±8.9	102.0 ±11.7	0.007	111.4 ±10.5	100.7 ±11.1	0.0006

a data for 25 subjects unavailable

Values are mean ± standard deviation or median (interquartile range).

For SI units multiply fibrinogen by 2.94; sTM by 1.0; CLT by 60; PAI-1 by 1.0; and TAFI activity by 10^3.

Abbreviations: α_2AP – α_2-antiplasmin, ACEIs – angiotensin-converting enzyme inhibitors, BMI – body mass index, CLT – clot lysis time, PAI-1 – plasminogen activator inhibitor 1, sTM – soluble thrombomodulin, TAFI – thrombin-activatable fibrinolysis inhibitor

values for sTM were 1.6–3.8 ng/ml. All measurements were performed by technicians blinded to the sample status. The coefficients of intra- and inter-assay variations were <7%.

Clot lysis time Fibrin CLT was measured using a tissue factor (TF)-induced lysis assay as described previously.[24] Briefly, citrated plasma was mixed with 15 mmol/l calcium chloride, 10 000-diluted human TF (Innovin, Dade Behring), 12 µmol/l phospholipid vesicles, and 60 ng/ml recombinant tissue-type plasminogen activator (tPA) (Boerhinger Ingelheim, Germany). Turbidity of this mixture was measured at 405 nm at 37°C.

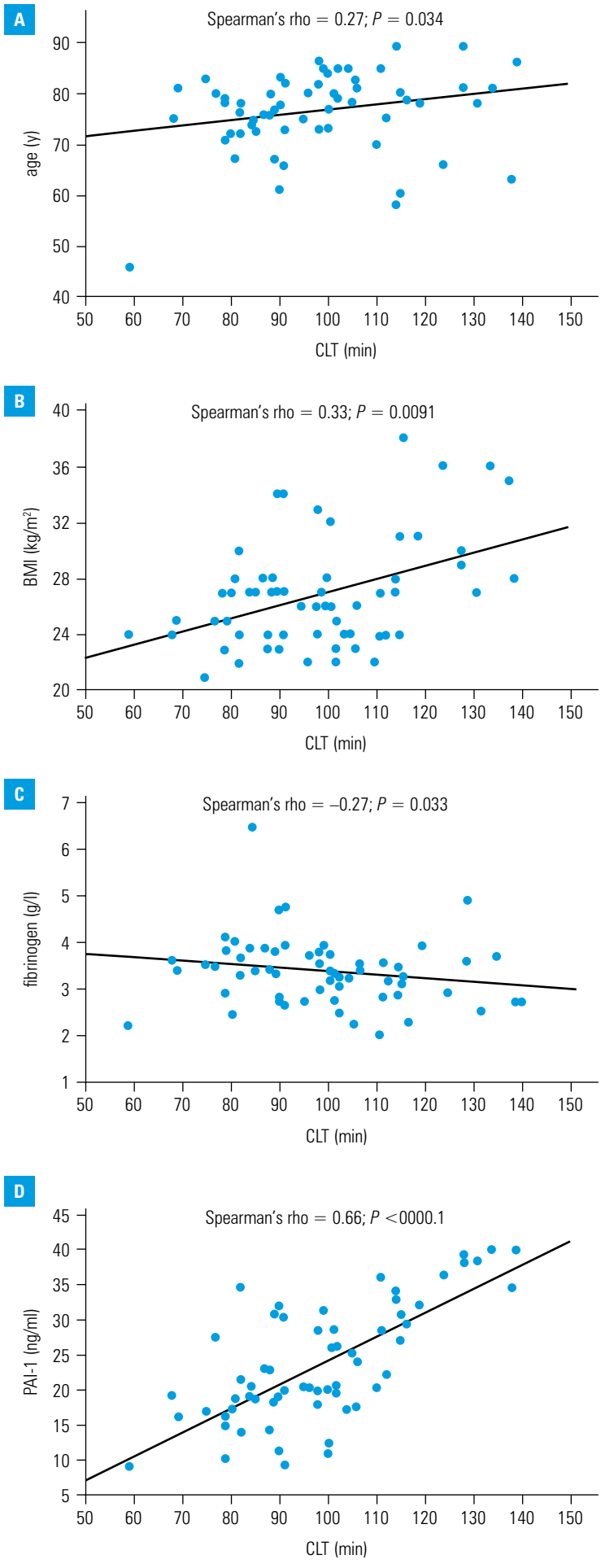


FIGURE Linear correlations of clot lysis time (A–H)
Abbreviations: see **TABLE**

CLT was defined as the time from the midpoint of the baseline clear to maximum turbid transition, to the final plateau phase. Normal values for CLT were 55–121 min. The intraindividual variability of CLT values was 7.4%.

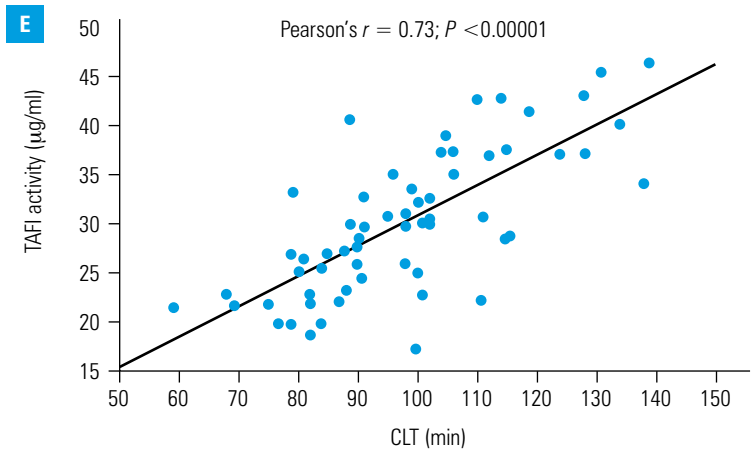
Echocardiography Standard transthoracic echocardiography was performed with the Acuson Sequoia C512 machine within 1 week preceding the blood collection. Left atrial (LA) diameter was evaluated.

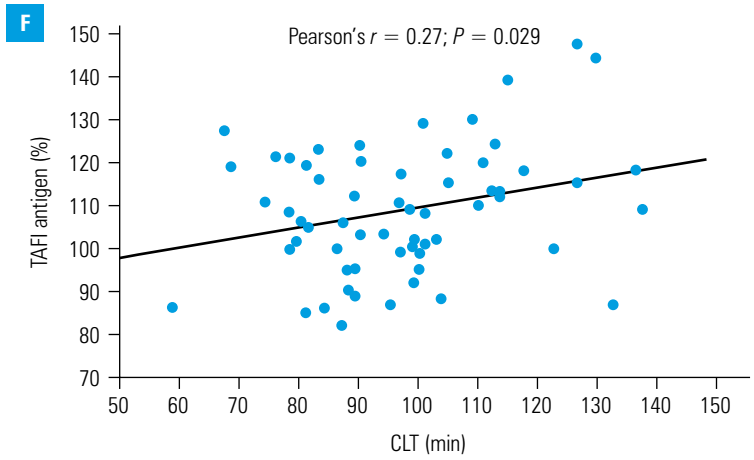
Statistical analysis Data were presented as mean and standard deviation or median and interquartile range as appropriate. Continuous variables were checked for normal distribution by the Shapiro-Wilk statistics and compared by the Student's *t* test for normal distributed or by the Mann-Whitney test for nonnormally distributed variables. Differences between multiple groups were compared with the analysis of variance or Kruskal-Wallis H-test, dependent on normal or nonnormal distribution, respectively. To assess linear dependence between variables, the Pearson correlation coefficient (Pearson's *r*) for normally distributed variables or Spearman's rank correlation coefficient (Spearman's rho) for nonnormally distributed variables were calculated. A *P*-value <0.05 was considered statistically significant.

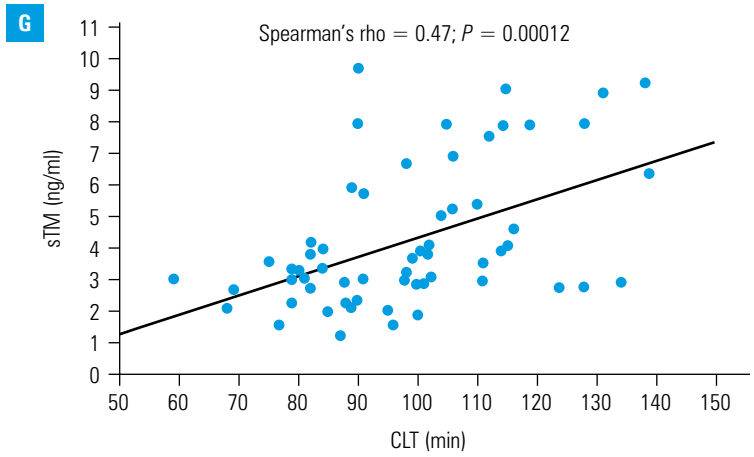
RESULTS A total of 62 patients with permanent nonvalvular AF (27 men and 35 women, aged 46–89 years) were studied. Demographic, clinical, and laboratory data were summarized in the **TABLE**. Mean CLT was 98.4 minutes (median, 98 min; range, 59–139 min). None of the patients was at low risk for ischemic stroke (CHA_2DS_2-VASc score of 0), 1 subject (1.6%) was at moderate risk (score 1), and 61 patients (98.4%) were at high risk for stroke (score of ≥2). There were differences for each CHA_2DS_2-VASc score point in CLT (P = 0.024), PAI-1 (P = 0.022), TAFI activity (P = 0.048), and sTM (P = 0.032, all *P*-values for trend); all 4 variables increased with higher scores. No such trends were observed for age, TAFI antigen, plasminogen, or antiplasmin levels.

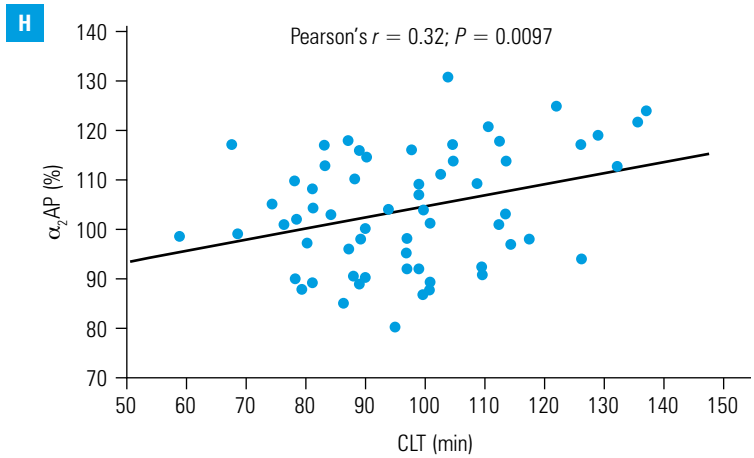
CLT correlated positively with age, body mass index, PAI-1 antigen, TAFI activity, TAFI antigen, α_2AP, and sTM (**FIGURE**). CLT showed an inverse correlation with plasma fibrinogen levels (**FIGURE**), but not with CRP. Time from the thrombotic event to blood collection was associated with plasminogen levels (Pearson's r = 0.49, P = 0.039) but not with CLT or other variables (data not shown).

There were no associations between LA diameter and the remaining variables (data not shown). The values of the LA diameter for 25 subjects were unavailable; however, no differences









in demographic, clinical, and laboratory data between the patients with and those without echocardiographic data were observed (data not shown).

To assess the effect of oral anticoagulation on fibrinolysis, we compared patients receiving such therapy (n = 46) vs. the remainder. Demographics, clinical factors, and other medications were similarly distributed in patients on vitamin K antagonists (VKA) and those not treated with VKA (data not shown). A median INR in anticoagulated patients was 2.3 (1.8–2.8). Of 46 patients treated with VKA, 3 individuals (6.5%) had INR below 1.2, 12 (26.1%) had INR between 1.21 and 1.99, 21 (45.7%) had INR between 2.0 and 3.0, and 10 (21.7%) had INR above 3.0. INR did not correlate with CLT, PAI-1, TAFI activity and antigen, α_2AP, or sTM (data not shown). Patients taking VKA had slightly higher sTM levels (3.6 [2.9–6.3] vs. 2.9 [2.2–4.1] ng/ml, $P = 0.049$) than the remaining subjects, while PAI-1, TAFI activity, TAFI antigen, α_2AP, and sTM did not differ between the 2 subgroups (data not shown).

Of 62 AF patients, there were 11 subjects (17.7%) with previous stroke. Among patients with previous stroke, all subjects (100%) were at high risk for ischemic stroke and 9 subjects (81.8%) were treated with VKA.

Of 62 AF patients, there were 19 subjects (30.6%) with any previous thrombotic event (stroke [n = 11], MI [n = 8], or PE [n = 3]). Among patients with any previous thrombotic event, all subjects (100%) were at high risk for ischemic stroke and 16 subjects (84.2%) were treated with VKA. There were no significant differences in demographics, risk factors, and medications between patients with previous stroke/any thrombotic event and the remaining subjects (TABLE). The only exception was a higher proportion of patients with CAD and a higher proportion of patients taking statins in the group with previous thrombotic event (TABLE). As shown in the TABLE, AF patients with previous stroke or any thrombotic event had higher CLT, PAI-1, TAFI activity, sTM, and α_2AP than the remaining subjects. AF patients with previous stroke had also higher TAFI antigen than those without a history of stroke.

DISCUSSION Our study has been the first to show that AF patients with previous stroke or any previous thrombotic event are characterized by impaired fibrin clot lysis associated with higher levels of PAI-1, TAFI, α_2AP, and sTM. The present study demonstrates that there are several similarities in determinants governing CLT in AF patients and those with venous thrombosis as well as in the general population.[17] Meltzer et al.[17] showed that hypofibrinolysis, which was explained by elevated levels of PAI-1, TAFI, plasminogen and tPA, is associated with the risk of venous thrombosis expressed as prolonged CLT. In AF patients, no effect of plasminogen was observed. We corroborated a major impact of PAI-1 and TAFI activity on

CLT values. It should be highlighted that patients with venous thromboembolism taking VKA were excluded from the analysis of CLT in the study by Meltzer et al.[17] Our findings suggest that when INRs are up to 4, CLT shows no association with this variable. Clot structure and lysis depend to some extent on coagulation factors, including those which are decreased by VKA.[25] Recently, it has been shown that VKA treatment increases clot permeability.[26] One might expect that AF patients taking VKA should have shorter CLT. We did not observe any differences between anticoagulated patients and the remainder. Moreover, the major effect of PAI-1, which is not affected by VKA, might blunt the effect produced by decreased prothrombin, FVII, FIX or FX, in anticoagulated AF patients.

Importantly, we have demonstrated longer CLT in relation to the previous thrombotic event, in particular with stroke. The CHA_2DS_2-VASc score correlated with CLT and its major determinants, which supports the concept that impaired fibrinolysis reflects an increased risk of stroke and thromboembolism in AF. In addition, it might be speculated that the effect of thrombotic manifestations on CLT is potent enough to be detectable in a relatively small patient population despite varying INRs. However, the study design made it impossible to show whether prolonged CLT is a marker of thromboembolism or a consequence of this complication. Of note, CLT was not correlated with LA diameter suggesting that its associations with fibrinolysis factors likely do not reflect local prothrombotic mechanisms in the LA. Impaired fibrinolytic potential in AF patients with a history of thrombotic events appears to be a persistent characteristic of a subgroup of patients with AF. A long follow-up is needed to assess whether recurrent thromboembolic events will be observed in these patients despite a fairly stable anticoagulant therapy.

Enhanced inflammatory state typical of AF patients and reflected by increased fibrinogen and CRP levels might affect clot lysis as shown for other plasma-based lysis assays.[27,28] In this study, concentrations of acute-phase proteins were similar in patients with a history of thromboembolism and the remainder. Moreover, no associations were found between CRP and CLT or other fibrinolytic proteins. It might be concluded that inflammation seems not to drive impairment of clot lysis in AF subjects.

It is important whether other drugs may affect clot lysis in AF patients. It has been shown that simvastatin, atorvastatin, and aspirin accelerate fibrin clot lysis using a different approach in which exogenous thrombin, together with recombinant tPA, is added to citrated plasma.[29,30] In this study, statins were administered often in the group of AF patients with previous thrombosis, and those AF patients had also prolonged CLT. We cannot exclude that those drugs affect CLT in AF patients; however, other potent prothrombotic mechanisms can overcome or blunt drug-mediated modulation of CLT.

We have shown higher frequency of CAD patients with AF in the group of subjects with previous thrombosis. Both AF and CAD are independently associated with prothrombotic state.[1,31] CAD coexists in 20% to 30% of patients with AF and may lead to complications during antithrombotic treatment following coronary interventions.[32] Impaired fibrinolysis in AF patients observed in the current study confirms that prothrombotic potential of AF, in particular complicated by thromboembolism, is potent and when combined with advanced atherosclerotic vascular disease, it requires VKA in combination with antiplatelet agents.

Interestingly, we have shown that there were differences in TAFI activity between patients with and without previous stroke or any thrombotic event, but TAFI antigen level was higher only in subjects with previous stroke. It has been shown that TAFI antigen levels are elevated during ischemic stroke and associated with impaired fibrinolysis measured using a different assay.[33]

To the best of our knowledge, this is the first report regarding TAFI in AF patients. Activated TAFI exerts an antifibrinolytic effect by removing C-terminal lysine residues from fibrin resulting in a decreased plasmin formation and a retardation of clot lysis.[34] This suggests an increased TAFI activation in AF patients with previous stroke or other thromboembolic event, which might represent a novel antifibrinolytic mechanism that operates in these individuals.

We reported higher α_2AP levels in AF subjects with previous thrombosis regardless of the anticoagulation status. However, plasminogen and α_2AP probably are not the limiting factors in fibrinolysis because they circulate at high concentrations in healthy subjects.[17]

This study has several limitations. Firstly, the size of the study group and the subgroups with previous stroke and all thrombotic events was limited, and the results of such analyses should be interpreted with caution. Secondly, all laboratory measurements were performed on a single occasion. We did not measure echocardiographic parameters other than LA diameter or coagulation factors and its inhibitors, including those dependent on vitamin K, that might affect CLT.[17] However, the current study was focused on fibrinolysis and its major determinants. Finally, a prospective study with follow-up is needed to show whether prolonged CLT predisposes to arterial thromboembolism in AF patients free of prior thromboembolic manifestations.

In conclusion, AF patients with previous stroke or any thrombotic event have impaired fibrinolysis mediated by PAI-1 and TAFI. This study confirms that AF complicated by thromboembolic events involves prothrombotic abnormalities including alterations attenuating the efficiency of fibrin clot lysis.

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REFERENCES

1 Roldán V, Marín F, Blann AD, et al. Interleukin-6, endothelial activation and thrombogenesis in chronic atrial fibrillation. Eur Heart J. 2003; 24: 1373-1380.

2 Sadanaga T, Kohsaka S, Ogawa S. D-dimer levels in combination with clinical risk factors can effectively predict subsequent thromboembolic events in patients with atrial fibrillation during oral anticoagulant therapy. Cardiology. 2010; 117: 31-36.

3 Roldán V, Marín F, Marco P, et al. Hypofibrinolysis in atrial fibrillation. Am Heart J. 1998; 136: 956-960.

4 Hatzinikolaou-Kotsakou E, Kartasis Z, Tziakas D, et al. Atrial fibrillation and hypercoagulability: dependent on clinical factors or/and on genetic alterations? J Thromb Thrombolysis. 2003; 16: 155-161.

5 Feinberg WM, Macy E, Cornell ES, et al. Plasmin-alpha2-antiplasmin complex in patients with atrial fibrillation. Stroke Prevention in Atrial Fibrillation Investigators. Thromb Haemost. 1999; 82: 100-103.

6 Cairns JA, Connolly S, McMurtry S, et al. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol. 2011; 27: 74-90.

7 Hart RG. What's new in stroke? The top 10 studies of 2006-2008. Part II. Pol Arch Med Wewn. 2008; 118: 747-755.

8 Freestone B, Lip GY, Chong AY, et al. Circulating endothelial cells in atrial fibrillation with and without acute cardiovascular disease. Thromb Haemost. 2005; 94: 702-706.

9 Califano F, Giovanniello T, Pantone P, et al. Clinical importance of thrombomodulin serum levels. Eur Rev Med Pharmacol Sci. 2000; 4: 59-66.

10 Adams TE, Huntington JA. Thrombin-cofactor interactions: structural insights into regulatory mechanisms. Arterioscler Thromb Vasc Biol. 2006; 26: 1738-1745.

11 Rau JC, Beaulieu LM, Huntington JA, Church FC. Serpins in thrombosis, hemostasis and fibrinolysis. Thromb Haemost. 2007; 5: 102-115.

12 Meltzer ME, Doggen CJ, de Groot PG, et al. Plasma levels of fibrinolytic proteins and the risk of myocardial infarction in men. Blood. 2010; 116: 529-536.

13 Jankun J, Skrzypczak-Jankun E. Yin and yang of the plasminogen activator inhibitor. Pol Arch Med Wewn. 2009; 119: 410-417.

14 van Tilburg NH, Rosendaal FR, Bertina RM. Thrombin activatable fibrinolysis inhibitor and the risk for deep vein thrombosis. Blood. 2000; 95: 2855-2859.

15 Montaner J, Ribo M, Monasterio J, et al. Thrombin-activable fibrinolysis inhibitor levels in the acute phase of ischemic stroke. Stroke. 2003; 34: 1038-1040.

16 Małyszko J, Tymcio J. Thrombin activatable fibrinolysis inhibitor and other hemostatic parameters in patients with essential arterial hypertension. Pol Arch Med Wewn. 2008; 118: 36-41.

17 Meltzer ME, Lisman T, de Groot PG, et al. Venous thrombosis risk associated with plasma hypofibrinolysis is explained by elevated plasma levels of TAFI and PAI-1. Blood. 2010; 116: 113-121.

18 Undas A, Zawilska K, Cieśla-Dul M, et al. Altered fibrin clot structure/function in patients with idiopathic venous thromboembolism and in their relatives. Blood. 2009; 114: 4272-4278.

19 Undas A, Nowakowski T, Cieśla-Dul M, et al. Abnormal plasma fibrin clot characteristics are associated with worse clinical outcome in patients with peripheral arterial disease and thromboangiitis obliterans. Atherosclerosis. 2011; 215: 481-486.

20 Undas A, Szułdrzynski K, Stępień E, et al. Reduced clot permeability and susceptibility to lysis in patients with acute coronary syndrome: effects of inflammation and oxidative stress. Atherosclerosis. 2008; 196: 551-557.

21 Undas A, Podolec P, Zawilska K, et al. Altered fibrin clot structure/function in patients with cryptogenic ischemic stroke. Stroke. 2009; 40: 1499-1501.

22 Meltzer ME, Doggen CJ, de Groot PG, et al. Reduced plasma fibrinolytic capacity as a potential risk factor for a first myocardial infarction in young men. Br J Haematol. 2009; 145: 121-127.

23 Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011; 342: d124.

24 Lisman T, Leebeek FW, Mosnier LO, et al. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. Gastroenterology. 2001; 121: 131-139.

25 Wolberg AS, Monroe DM, Roberts HR, et al. Elevated prothrombin results in clots with an altered fiber structure: a possible mechanism of the increased thrombotic risk. Blood. 2003; 101: 3008-3013.

26 Blombäck M, He S, Bark N, et al. Effects on fibrin network porosity of anticoagulants with different modes of action and reversal by activated coagulation factor concentrate. Br J Haematol. 2001; 152: 758-765.

27 Undas A, Stępień E, Tracz W, et al. Lipoprotein(a) as a modifier of fibrin clot permeability and susceptibility to lysis. J Thromb Haemost. 2006; 4: 973-975.

28 Undas A, Plicner D, Stepień E, et al. Altered fibrin clot structure in patients with advanced coronary artery disease: a role of C-reactive protein, lipoprotein(a) and homocysteine. J Thromb Haemost. 2007; 5: 1988-1990.

29 Undas A, Celinska-Löwenhoff M, Löwenhoff T, et al. Statins, fenofibrate, and quinapril increase clot permeability and enhance fibrinolysis in patients with coronary artery disease. J Thromb Haemost. 2006; 4: 1029-1036.

30 Undas A, Topór-Mądry R, Tracz W. Simvastatin increases clot permeability and susceptibility to lysis in patients with LDL cholesterol below 3.4 mmol/l. Pol Arch Med Wewn. 2009; 119: 354-359.

31 Butenas S, Undas A, Gissel MT, et al. Factor XIa and tissue factor activity in patients with coronary artery disease. Thromb Haemost. 2008; 99: 142-149.

32 Wrigley BJ, Tapp LD, Shantsila E, et al. Antithrombotic therapy in anticoagulated patients with atrial fibrillation presenting with acute coronary syndromes and/or undergoing percutaneous coronary intervention/stenting. Pol Arch Med Wewn. 2010; 120: 290-293.

33 Rooth E, Wallen H, Antovic A, et al. Thrombin activatable fibrinolysis inhibitor and its relationship to fibrinolysis and inflammation during the acute and convalescent phase of ischemic stroke. Blood Coagul Fibrinolysis. 2007; 18: 365-370.

34 Wang W, Boffa MB, Bajzar L, et al. A study of the mechanism of inhibition of fibrinolysis by activated thrombin-activable fibrinolysis inhibitor. J Biol Chem. 1998; 273: 27176-27181.

ARTYKUŁ ORYGINALNY

Wydłużony czas lizy skrzepu u chorych z utrwalonym migotaniem przedsionków po przebytych incydentach akrzepowo-zatorowych

Michał Ząbczyk[1], Jacek Majewski[2], Jacek Lelakowski[2]

1 Zakład Kardiochirurgii, Anestezjologii i Kardiologii Doświadczalnej, Instytut Kardiologii, Uniwersytet Jagielloński, Collegium Medicum, Krakowski Szpital Specjalistyczny im. Jana Pawła II, Kraków
2 Klinika Elektrokardiologii, Instytut Kardiologii, Uniwersytet Jagielloński, Collegium Medicum, Krakowski Szpital Specjalistyczny im. Jana Pawła II, Kraków

SŁOWA KLUCZOWE

choroba zakrzepowo-zatorowa, czas lizy skrzepu, fibrynoliza, migotanie przedsionków, udar niedokrwienny mózgu

STRESZCZENIE

WPROWADZENIE Migotanie przedsionków (*atrial fibrillation* – AF) wiąże się ze skłonnością do występowania incydentów zakrzepowo-zatorowych.

CELE Badano zależności pomiędzy przebytymi epizodami zakrzepowo-zatorowymi a parametrami układu fibrynolizy u chorych z AF.

PACJENCI I METODY W badaniu obserwacyjnym analizowano 62 kolejnych chorych z utrwalonym AF (27 mężczyzn i 35 kobiet w wieku 46–89 lat [mediana wieku wynosiła 78 lat]). Z badania nie wykluczano chorych stosujących przewlekle warfarynę lub acenokumarol. Oceniano czas lizy skrzepu fibrynowego (*clot lysis time* – CLT), stężenie antygenu inhibitora aktywatora plazminogenu (*plasminogen activator inhibitor-1* – PAI-1), stężenie antygenu oraz aktywność inhibitora fibrynolizy aktywowanego przez trombinę (*thrombin-activatable fibrinolysis inhibitor* – TAFI), stężenie plazminogenu, α_2-antyplazminy (α_2AP) oraz rozpuszczalnej trombomoduliny (*soluble thrombomodulin* – sTM).

WYNIKI W grupie chorych z AF u 19 osób (30,6%) występował incydent zakrzepowy w wywiadzie (u 11 chorych udar niedokrwienny mózgu, u 8 zawał serca, u 3 zator tętnicy płucnej). U tych chorych stwierdzono wydłużony CLT ($p = 0,0035$ u chorych po udarze mózgu oraz $p = 0,001$ u chorych po przebytym jakimkolwiek incydencie zakrzepowym) wraz ze zwiększonym stężeniem PAI-1 (odpowiednio $p = 0,025$ i $p = 0,016$), zwiększoną aktywnością TAFI (odpowiednio $p = 0,002$ oraz $p = 0,011$), zwiększonym stężeniem sTM (odpowiednio $p = 0,0023$ i $p = 0,012$), a także α_2AP (odpowiednio $p = 0,007$ i $p = 0,0006$), w porównaniu z pozostałymi pacjentami. U chorych z AF po przebytym udarze mózgu stwierdzono także większe stężenie antygenu TAFI w porównaniu z pozostałymi chorymi ($p = 0,04$). CLT ($p = 0,024$), stężenie PAI-1 ($p = 0,022$), aktywność TAFI ($p = 0,048$) oraz stężenie sTM ($p = 0,032$; wartości p dla trendów) zwiększały się wraz z rosnącą punktacją skali CHA_2DS_2-VASc. CLT nie korelował z okresem pomiędzy wystąpieniem incydentu zakrzepowego a włączeniem do badania. Wśród chorych przyjmujących doustne antykoagulanty ($n = 46$) stwierdzono nieco zwiększone stężenia sTM (3,6 [2,9–6,3] *vs* 2,9 [2,2–4,1] ng/ml; $p = 0,049$) w porównaniu z pozostałymi chorymi.

WNIOSKI Przebyty udar niedokrwienny mózgu lub inny incydent zakrzepowo-zatorowy u chorych z AF wiąże się z osłabioną zdolnością lizy wytworzonego skrzepu fibrynowego oraz zwiększonymi stężeniami PAI-1, TAFI, sTM oraz α_2AP.

Adres do korespondencji:
mgr Michał Ząbczyk, Instytut Kardiologii, Uniwersytet Jagielloński, Collegium Medicum, ul. Prądnicka 80, 31-202 Kraków, tel.: 12-614-31-43, fax: 12-614-31-43, e-mail: michalzabczyk@op.pl
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