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The Role of D-Dimer in the Diagnosis of Left Atrial Appendage Thrombus in Patients with Atrial Fibrillation

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ABSTRACT

Objectives: The aim of this study was to evaluate the ability of D-Dimer for the diagnosis of left atrial appendage (LAA) thrombus in patients with chronic atrial fibrillation (AF).

Methods: 80 patients with chronic AF who fulfilled the inclusion and exclusion criteria were studied prospectively. 45 patients had LAA thrombus diagnosed by transesophageal echocardiography (TEE) constituted group I (LAA thrombus group). The other 35 patients without LAA thrombus constituted group II. All the 45 patients (100%) in group I with LAA thrombus had elevated D-Dimer levels while only 10 patients (28.5%) in group II without LAA thrombus had elevated D-Dimer levels ($P < 0.001$). All the patients received oral anticoagulation with warfarin keeping the INR between 2 and 3 for 3 months. TEE was done to all the patients at 3-month follow up.

Results: 12 patients (26.7%) in group I had elevated D-Dimer levels. The number of patients with positive D-Dimer decreased significantly at 3-month follow up ($P < 0.001$) while on warfarin. LAA thrombus resolved completely in 35 patients (77.8%) at 3-month follow up. In group II, all the 35 patients (100%) had negative D-Dimer levels at 3-month follow up. At 6-month follow up all the patients in group I and II had negative D-Dimer levels (100%).

Conclusion: The sensitivity of D-Dimer for the diagnosis of LAA thrombus is 100%. The specificity of D-Dimer for the diagnosis of LAA thrombus is 71.4%. So, patients with positive and elevated D-Dimer levels should undergo TEE for the diagnosis of LAA thrombus. While a negative D-Dimer test result makes the diagnosis of LAA thrombus is extremely unlikely. Appropriate oral anticoagulation results in complete resolution of LAA thrombus within 6 months.

Keywords: Chronic atrial fibrillation; D Dimer; Left atrial thrombi; marevan; warfarin; transesophageal echocardiography.

Abbreviations: Atrial fibrillation (AF); transesophageal echocardiography (TEE); left atrial appendage (LAA)

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INTRODUCTION

D-Dimer is a cross-linked peptide derived from fibrin thrombus. In vivo, fibrin clot normally undergoes fibrinolysis by plasmin, which releases D-Dimer as a specific fibrin-splitting product. Thus D-Dimers are elevated in patients who have formed clots [(1)]. D-Dimer is a laboratory index of thrombogenesis [(2)].

There is no laboratory test to aid the diagnosis of LAA thrombi, D-Dimers may have the potential role as a non-invasive marker of the presence of thrombi and risk for thrombo-embolism [(3)].

Aim of the work: To evaluate the ability of D-Dimer for the diagnosis of LAA thrombus in patients with chronic AF.

PATIENTS AND METHODS

100 consecutive patients with chronic AF who were referred for TEE to diagnose or to rule out the presence of left atrial (LA) thrombus were studied prospectively at the NHI during the period between June 2008 and January 2011.

Exclusion criteria

1. Patients with any thromboembolic events within the previous 2 months, patients with deep venous thrombosis or pulmonary embolism.
2. Patients with disseminated intravascular coagulation (DIC), malignancies, infections, liver diseases, renal failure, collagen vascular disease, aortic dissection, acute coronary syndromes, or pregnant patients.
3. Patients with recent trauma or surgery (of less than one month).
4. Patients receiving anticoagulant therapy.
5. Patients with any contraindication to anticoagulants.
6. Patients with any intracardiac masses or thrombi, except those with LAA thrombi.
7. Patients who were not presented at follow up.

- Every patient was subjected to:

1. Complete history taking.
2. Clinical examination.
3. ECG.
4. Chest X-Ray.
5. Transthoracic Echocardiography (TTE).
6. TEE:

- was done using multiplane probe.
- LAA thrombus: was defined as the presence of any echogenic mass with the following characteristics: clearly defined border, visibility in 2 anatomic planes and with echo density distinct from the adjacent myocardium [(4)].

7. Blood sampling procedure:

- Blood samples were drawn immediately before TEE and at follow up.
- D-Dimer levels were measured (using the Latex Agglutination test- Elisa kit). D-Dimer level was considered negative if a level of < 0.5μg/ml was detected.
- 3-Month follow up:
- All the patients received oral anticoagulation with warfarin (as part of the clinical management) keeping the INR between 2 and 3 for 3 months.

  D-Dimer levels were measured to all the patients at 3-month follow up.
- TEE was done to all the patients at 3-month follow up.

6-Month follow up:

- All the patients continued receiving oral anticoagulation (warfarin) keeping the INR between 2 and 3 for another 3 months.
- D-Dimer levels were measured to all the patients at 3-month follow up.
- TEE was done to all the patients at 3-month follow up.
- Informed consent was obtained from the patients.

STATISTICAL ANALYSIS

- Quantitative data were expressed as mean ± standard deviation.
- Student's t test was used to compare quantitative data between 2 groups.
- Discrete variables were compared with Chi squared and Fisher's exact test.
- A value of $P < 0.05$ was considered statistically significant. $P < 0.01$ was considered highly significant.

RESULTS

- 100 consecutive patients with chronic AF who were referred for TEE to diagnose or to rule out the presence of LA thrombus were studied prospectively.
- 15 patients were excluded from the study because they had LA cavity thrombus. Another 5 patients were excluded from the study because they had mobile LAA thrombus. All these 20 patients were referred for surgery. So, the study population consisted of 80 patients who fulfilled the inclusion and exclusion criteria for this study.
- 45 patients had LAA thrombus diagnosed by TEE. The other 35 patients had no LAA thrombus.
- The 45 patients with LAA thrombus constituted group I (LAA thrombus group). Of them, 19 patients (42.2%) had history of cerebral infarction, 15 patients (33.3%) had history of transient ischemic attack (TIA), and 11 patients (24.5%) had mitral stenosis (MS).
- The 35 patients without LAA thrombus constituted group II (Control group). Of them, 16 patients (45.7%) had history of cerebral infarction, 11 patients (31.4%) had history of TIA, and 8 patients had MS.
- No statistically significant difference was found between the 2 groups as regards the proportion of different categories of patients studied.

1. The baseline clinical characteristics

Group I: (LAA thrombus group)

Atrial

Fig 1: Left atrial thrombus in a patient with atrial fibrillation and high D Dimer. Thrombus disappeared with warfarin as TEE 3 and 6 months later proved it

Fig 2: Left atrial thrombus in a patient with atrial fibrillation and high D Dimer. TEE after 3 and 6 months proved complete resolution of thrombus on warfarin therapy.

Their age ranged from 29.0 to 71.0 years old with a mean of 49.8±14.8 years. 25 patients (55.5%) were females (F) and 20 patients (44.5%) were males. 25 patients (55.5%) were diabetics (DM). 28 patients (62.2%) were hypertensives at presentation (HTN). 11 patients (24.4%) had dyslipidemia. 26 patients (57.7%) were smokers. LAD ranged from 4.30 cm to 5.90 cm with a mean of 5.10±0.57cm. LASEC was found in all the 45 patients (100%). LV ejection fraction (LVEF) ranged from 49.0% to 67.0% with a mean of 58.0 ± 7.0%. 28 patients (62.2%) were on antiplatelet therapy. One patient (2.2%) had significant (moderate to severe) mitral regurgitation (MR).

Group II: (Control group)

- Their age ranged from 31.0 to 74.0 years old with a mean of 52.0±14.1 years. 19 patients (54.3%) were females (F) and 16 patients (45.7%) were males. 20 patients (57.1%) were diabetics. 23 patients (65.7%) were hypertensives at presentation (HTN). 9 patients (25.7%) had dyslipidemia. 21 patients (60%) were smokers. LAD ranged from 4.10cm to 5.70cm with a mean of 4.90±0.63cm. LASEC was present in 32 patients (91.4%). LVEF ranged from 51.0% to 69.0% with a mean of 60.0±6.9%. 23 patients (65.7%) were on antiplatelet therapy. One patient (2.8%) had significant (moderate to severe) MR.
- No statistically significant difference was found between the 2 groups as regards the baseline clinical characteristics. (Table 1)

Table 1: Baseline clinical characteristics in Both groups

	Group I LAA thrombus (45)	Group II Control (35)	P Value
Age	49.8 ± 14.8	52.0 ± 14.1	NS
Gender (F)	25 (55.5%)	19 (54.3%)	NS
DM	25 (55.5%)	20 (57.1%)	NS
HTN	28 (62.2%)	23 (65.7%)	NS
Dyslipidemia	11 (24.4%)	9 (25.7%)	NS
Smoking	26 (57.7%)	21 (60.0%)	NS
LAD	5.10 ± 0.57	4.90 ± 0.63	NS
LASEC	45 (100%)	32 (91.4%)	NS
LVEF	58.0 ± 7.0%	60.0 ± 6.9%	NS
Antiplatelet therapy	28 (62.2%)	23 (65.7%)	NS
Significant MR	1 (2.2%)	1 (2.8%)	NS

2. D-Dimer

Group I:

- All the 45 patients (100%) in group I with LAA thrombus had positive D-Dimer levels.
- D-Dimer levels were elevated in all the patients with a mean of 4.0±3.2 µg/ml.

Group II:

- Only 10 patients (28.5%) in group II without LAA thrombus had positive D-Dimer levels.
- D-Dimer levels were elevated in these 10 patients with a mean of 1.9±1.3 µg/ml. The other 25 patients had negative D-Dimer levels.

- Comparison between the 2 groups as regards D-Dimer levels:

- D-Dimer levels were positive and elevated in all the patients in group I (100%) versus 10 patients (28.5%) in group II, P < 0.001. Fig. (3)

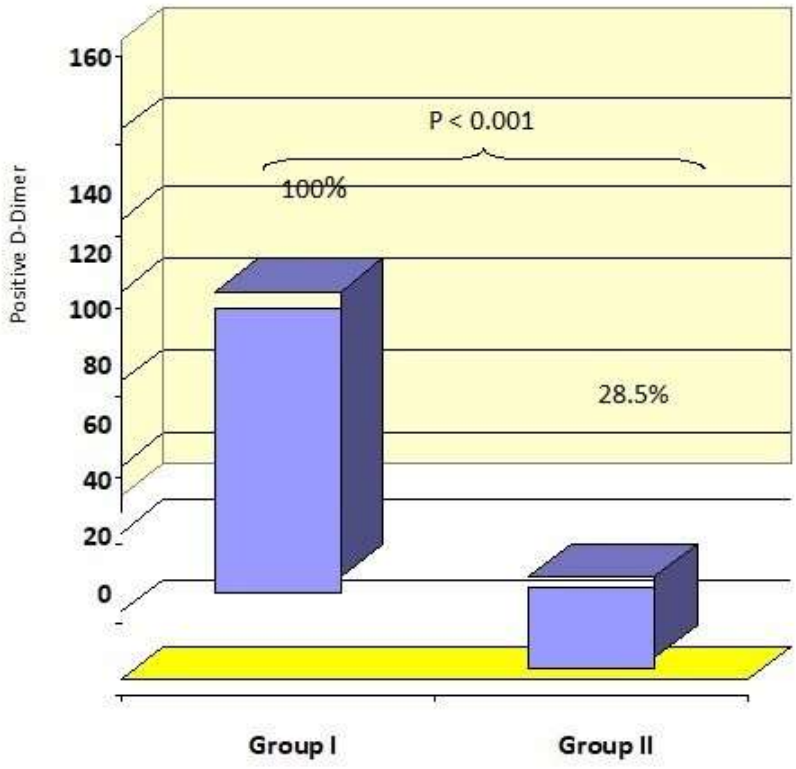

Fig 3: Comparison between the two groups as regards D Dimer

- Mean D-Dimer level was significantly higher in the 45 patients with positive test in group I than in the 10 patients with positive test in group II (P < 0.05).
- (B) The diagnostic value of D-Dimer in LAA thrombus:
- All the 45 patients with LAA thrombus had positive and elevated D-Dimer levels.
- 10 of the 35 patients without LAA thrombus had positive and elevated D-Dimer levels.
- So, the sensitivity of D-Dimer for the diagnosis of LAA thrombus was 100%.
- The specificity of D-Dimer for the diagnosis of LAA thrombus was 71.4%.

3. Follow up (3 months)

A) Anticoagulant therapy:

- All the patients in both groups received oral anticoagulation with warfarin keeping the INR between 2 and 3 for 3 months.
- No embolic or hemorrhagic complications occurred during these 3 months.
- B) TEE:
- TEE was done to all the patients in both groups at 3-month follow up.
- Group I:
- 12 patients (26.7%) had positive D-Dimer levels. The other 33 patients (73.3%) had negative D-Dimer levels.
- The number of patients with positive D-Dimer decreased significantly at 3-month follow up, P < 0.001 (Fig 4).
- D-Dimer levels were elevated in these 12 patients with a mean of 1.75±1.20µg/ml.
- Mean D-Dimer level decreased significantly in these 12 patients from 7.33±1.60µg/ml at presentation to 1.75±1.20µg/ml at 3-month follow up, P < 0.001 (Fig 5).
- So, anticoagulant therapy resulted in a significant decrease in mean D-Dimer levels after 3 months.
- LAA thrombus resolved completely in 35 patients (77.8%) at 3-month follow up

Group II:

- All the 35 patients (100%) in group II had negative D-Dimer levels.
- So, anticoagulant therapy resulted in normalization of D-Dimer levels at 3-month follow up in all the patients.

4. Follow up (6 months)

A) Anticoagulant therapy:

- All the patients in both groups continued on warfarin keeping the INR between 2 and 3 for another 3 months.
- No emboli or hemorrhagic complications occurred during the 6-month follow up period.
- (B) TEE:
- TEE was done to all the patients in both groups at 6-month follow up.

- Group I:
- All the patients had negative D-Dimer levels (100%).
- So, anticoagulant therapy resulted in normalization of D-Dimer levels in all the patients.
- LAA thrombus resolved completely in all the patients (100%)

Group II:

* All the patients had negative D-Dimer levels (100%).

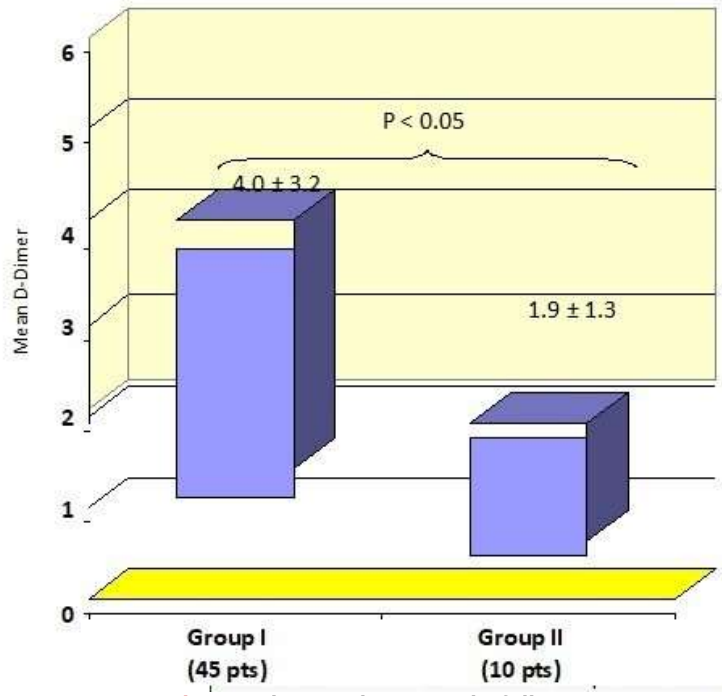

Fig 4: D Dimer at three months follow up

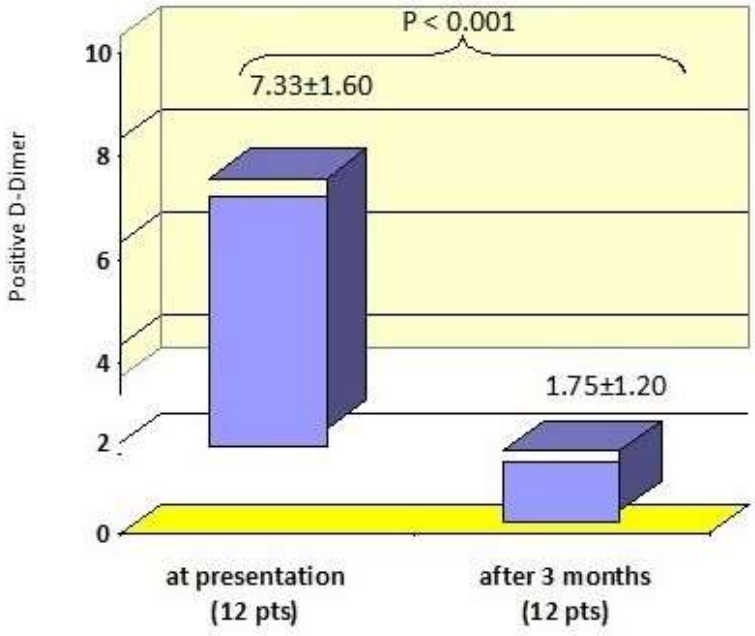

Fig 5: D-Dimer at 3-month follow up.

DISCUSSION

D-Dimer, an indirect marker of fibrin formation, has been demonstrated to be a sensitive marker of activation of coagulation in various clinical conditions [5].

In the present study, 45 patients with LAA thrombus constituted group I (LAA thrombus group). 35 patients without LAA thrombus constituted group II (Control group). The result of the present study is in agreement with the results of Habara et al., [3] who reported increased D-Dimer levels in patients with LAA thrombus. Also, in accordance with the result of the present study, Hayoshi, [6], and Sakoi et al., [7], reported significant increase in D-Dimer levels in patients with LA and LAA thrombi.

In the present study, D-Dimer levels were positive and elevated in all the patients (100%) with LAA thrombus (Group I) versus 10 patients (28.5%) in the control group (Group II). Similar results were reported by Habara et al., [3].

In the present study, the sensitivity of D-Dimer for the diagnosis of LAA thrombus was 100% and the specificity was 71.4%. Similar results were reported by Habara et al., [3]. So, the results of the present study indicated that patients with positive and elevated D-Dimer levels should undergo TEE for the diagnosis of LAA thrombus. While a negative D-Dimer test makes the diagnosis of LAA thrombus is extremely unlikely. This result is in agreement with the results of Habara et al., [3] who concluded that D-Dimer is a reliable parameter to exclude the presence of atrial thrombi in patients with AF.

It has been reported that elevated D-Dimer could also be present in patients who are forming and degrading fibrin at abnormally high rate but who do not have evidence of a clot [8-10]. Habara et al., [3] demonstrated that patients with AF show significant increases in plasma D-Dimer level, suggesting the presence of a hypercoagulable or pro-thrombotic state. In agreement with the result of the present study, Lip et al., [2], Habara et al., [3] and Cohen et al., [11], reported a nearer percentage of increase in D-Dimer levels in patients with AF.

Since D-Dimer is a laboratory index of thrombogenesis [2,3,5,11], so, all the patients in both groups in the present study received adequate oral anticoagulation with warfarin keeping the INR between 2 and 3 for 3 months.

In group II, anticoagulant therapy resulted in normalization of D-Dimer levels after 3 months in all the patients. Similarly, Lip et al., [2] reported a significant reduction in D-Dimer levels at 2 months after the introduction of warfarin. Also, the same result was reported by Habara et al., [3] and Cohen et al., [11]. The explanation for the complete normalization of D-Dimer levels in group II in the present study in comparison to group I which showed a significant decrease in D-Dimer levels is due to the presence of LAA thrombi in group I. So, warfarin treatment is effective in preventing excessive fibrin turnover, consistent with the antithrombotic effects of warfarin [2,3,11].

Also, in the present study, LAA thrombus resolved completely in 35 patients (77.8%) at 3-month follow up. We didn't find in the literature any report giving anticoagulation for 6 months to these patients to compare the result of the present study with.

In the present study, LAA thrombus resolved completely in all the patients (100%) at 6-month follow up. This result was reported by many investigators [12-17].

CONCLUSIONS AND RECOMMENDATIONS

1. D-Dimer levels are positive and elevated in all the patients with LAA thrombus.
2. The sensitivity of D-Dimer for the diagnosis of LAA thrombus is 100%. The specificity of D-Dimer for the diagnosis of LAA thrombus is 71.4%. So, patients with positive and elevated D-Dimer levels should undergo TEE for the diagnosis of LAA thrombus. While a negative D-Dimer test result makes the diagnosis of LAA thrombus is extremely unlikely.
3. Appropriate oral anticoagulation results in complete resolution of LAA thrombus within 6 months.

- It is recommended to do D-Dimer test to all the patients with suspected LAA thrombus as a part of their initial assessment.

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