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Case Report

Left Atrial Thrombus Resolution Using Unfractionated Heparin and Warfarin in a Patient with Mitral Stenosis

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Abstract

Background: Though the use of Low Molecular Weight Heparin (LMWH) in general is preferred due to its convenient and eliminates the need for activated Partial Thromboplastin Time (aPTT) monitoring but Unfractionated Heparin (UFH) is still widely used in clinical setting due to its availability and low price. Besides UFH, the use of oral anticoagulant therapy with warfarin, has been the standard therapy for the prevention of thromboembolism in patients with AF. Our aim is to report a case of the resolution of left atrial thrombus in a patient with mitral stenosis.

Case Illustration: A Case report of a female patient aged 54 years who admitted with a sudden neurological deficits and mitral stenosis with atrial fibrillation. Bedside transthoracal echocardiography (TTE) showed mobile thrombus which moved and obstructed the mitral valve during diastolic phase. Unfractionated heparin (UFH) was administered 3000 unit bolus intravenously and maintained with 600 unit per hour for five days and warfarin 2 mg was initiated two days after the first UFH administration. TTE evaluation showed the resolution of LA thrombus.

Conclusion: The administration of the combination of UFH and warfarin had successfully caused resolution of the LA thrombus and prevented the patient from surgical intervention. This case report indicated that Unfractionated Heparin and Warfarin were still the treatments option in LA thrombus patients with mitral stenosis and atrial fibrillation.

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Key words : Left atrial thrombus, unfractionated heparin, thrombus resolution

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Introduction

The highest incidence of left atrial (LA) thrombus is in patients with rheumatic mitral stenosis and atrial fibrillation. LA thrombi tend to form when there is stasis of blood flow in the left atrium (LA). In general, low-velocity flow in the LA is associated with atrial enlargement, mitral valve disease, atrial fibrillation (AF).[1] It is well known that AF, which causes LA thrombus that may produce

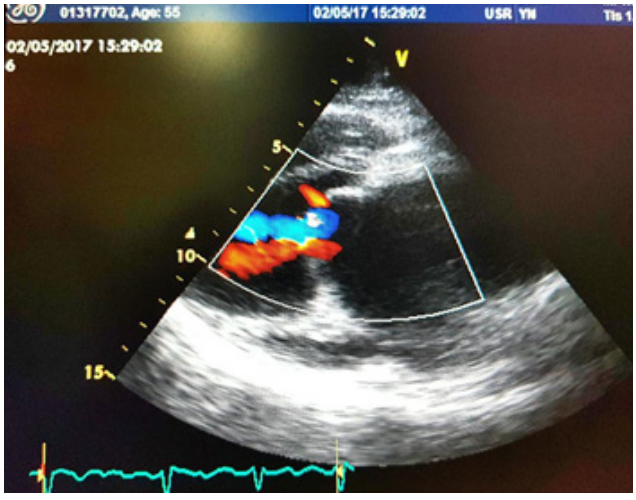

Figure 1. Echocardiography showing severe mitral stenosis

an embolism, is a common cause of an ischemic stroke, and that AF-related strokes are accompanied by severe neurological deficits, disability and high mortality.[2]

Unfractionated Heparin (UFH), traditionally the backbone of antithrombotic therapy, is a heterogeneous mucopolysaccharide on blood vessels. The major of UFH is on the interaction of antithrombin and thrombin (factor IIa), to inhibit the thrombin induced platelet aggregation that initiates acute coronary syndrome and venous thrombosis.[3] Serial transesophageal echocardiography (TEE) has demonstrated the dissolution of intracardiac thrombi with anticoagulant therapy. Besides UFH, the use of oral anticoagulant therapy with warfarin, described as a vitamin K antagonist (VKA), has been the standard therapy for the prevention of thromboembolism in patients with AF.[4,5] Novel oral anticoagulants (NOACs) were developed as an alternative to vitamin K antagonists and several studies have evaluated the ability of NOAC to decrease clotting as well as the risk of major bleeding in comparison to vitamin K antagonists, such as warfarin. They have a decreased risk of significant bleeding and other secondary adverse events.[6] However there is no clear guidelines or consensus for the management of left atrial thrombus in rheumatic mitral stenosis with atrial fibrillation and acute ischemic stroke. If an LA/LAA thrombus is detected on a TEE, current guidelines recommend vitamin K antagonist (VKA) treatment with a therapeutic international normalized ratio (INR) of 2.0 to 3.0 for at least 3 weeks and a follow-up TEE to ensure thrombus resolution prior to interventions [7,8]

This is a case report of a patient presented with acute stroke due to valvular atrial fibrillation due to mobile left atrial thrombus which resolved after UFH and warfarin administration.

Case illustration

A female patient 54 years old, admitted to Emergency Department of Tarakan Hospital in Jakarta with a sudden onset of slurred speech and left sided hemiparesis accompanied with shortness of breath which worsened one day prior to admission accompanied with palpitation and feeling weakness. Fatigue during activity occurred for the last one week with orthopnea and abdominal discomfort. The patient had never had these complaints before. She was known as an active teacher for nearly thirty years. She had never taken any particular medicine or herbal substances. She was a married lady and had three children with previously normal deliveries.

From physical examination, patient looked severely ill, clouding consciousness with blood pressure 110/70 mmHg, the heart rate was 134 times per minute irregular, the respiratory rate was 30 times per minutes, and the temperature was 36.7 degree Celsius.

Conjunctiva palpebral anemic and scleral icteric were not found with the distension of jugular vein. The first heart sound increased in intensity with mid diastolic murmur III/6 at apex and irregular heartbeat. The lungs sound was vesicular with rales in both basal

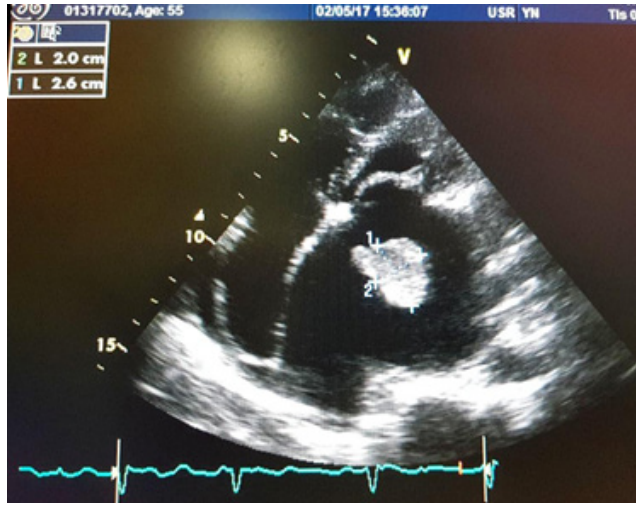

Figure 2. The apical four chamber view showed LA thrombus "flying" in the center of the left atrium

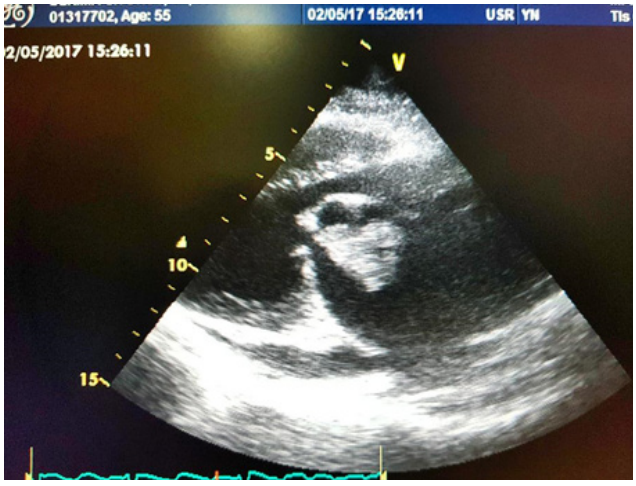

Figure 3. Parasternal long axis view showed LA thrombus moved closer to stenosis mitral valve

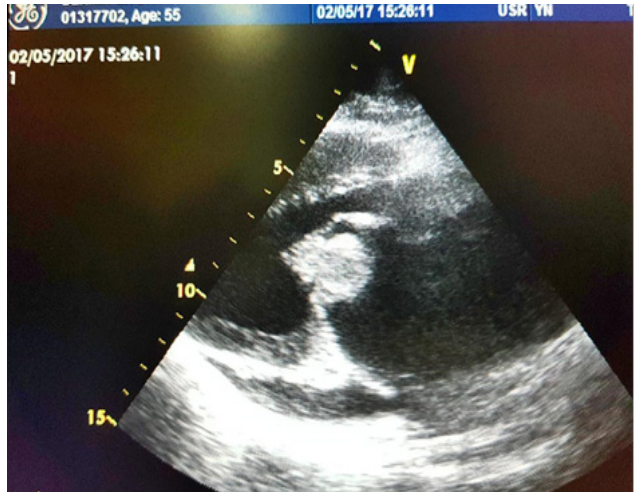

Figure 4. The LA thrombus moved obstructing the mitral valve area during diastole phase

sides. The abdomen was soft with hepatomegaly and normal peristaltic. Both extremities were warm with pretibial edema.

The electrocardiography examination was atrial fibrillation with QRS rate was 144 beat per minutes, QRS axis was RAD, QRS duration was normal with RVH.

The chest X ray looked cardiomegaly with CTR was 70% with normal aortic and pulmonary segments, apex was downward with double contour appearance. The laboratory findings showed normal limits.

Bed side echocardiography revealed dilated left atrium, normal left ventricular function (LVEF = 67%), reduced right ventricular function (TAPSE = 1.4 cm), global normokinetic wall motion, mild calcified RCC and NCC of aortic valve with normal function, mitral valve looked dooming with Wilkins'score was 7 (Valve Thickening = 2, Leaflet mobility = 1, valvular Calcification = 2, subvalvular thickening = 2) with mitral valve area was 0.7 cm2, mean mitral valve gradient was 8 mmHg, trivial tricuspid regurgitation and mild pulmonary regurgitation (Fifure 1) Mobile left atrial thrombus was found with diameter 20 x 35 mm (figure 2) and sometimes obstructed the mitral valves area during diastolic phase (Figure 3 and 4).

The patient was diagnosed as acute stroke with severe mitral stenosis - NYHA FC IV- with left atrial thrombus and atrial fibrillation rapid ventricular response. The treatment of this patient was bed rest – semifowler position with O2 3 l/ minutes, furosemide injection bolus 40 mg intravenously (iv), maintenance 2 x 20 mg/ iv, digoxin 0.50 mg drips intravenously, continued with digoxin 0.25 mg orally, spironolactone 25 mg, unfractionated heparin (UFH) with initial dose of 3000 unit bolus intravenously, and maintained intravenous drips with the dosage of 600 unit per hour for five days. Oral anti coagulation warfarin 2 mg was given two days after the first initiation of unfractionated heparin. Activated plasma thromboplastin time (aPTT) was monitored every six hours since the initial administration with normal range varied between 1.5 to 1.7 times compared to the control value. She was consulted to the neurologist for further management and was administered with citicholin 2 x 1 gr intravenously, piracetam 3 x 3 gr intravenously, and atorvastatin 20 mg orally. The patient was also consulted to the cardiac surgeon planned for mitral valve replacement and thrombus evacuation.

While waiting for surgery, the patient showed improvement of the neurological status. As the preparation to surgery, patient underwent coronary angiography with normal result.

After 5 days of UFH administration and 3 days treated with warfarin 2 mg, prothrombin time (PT) and the international normalized ratio (INR) were evaluated and showed expected target (INR 2.6). No complication such as bleeding or bruising occurred during the administration of both anticoagulant. No signs of neurological deficits showed during the administration of UFH and warfarin. Echocardiography examination was performed for post anticoagulant treatment and showed severe mitral stenosis (figure 5). No LA

thrombus found instead of showing a reduced density of LASEC (Figure 6).

The patient didn't undergo surgical management and had continuous oral medical treatment instead. She had a regular control at the heart clinic with stable condition and was performed the transesophageal echocardiography (TEE) five months after the acute stroke attack. The TEE concluded that MS severe was found with Wilkins Score 7; LA SEC and left atrial appendage SEC (LAA SEC) was detected without any thrombus (figure 7). The patient had warfarin (INR target 2.5 -3) and other medications for another four weeks and TEE evaluation was performed because the patient was planned to undergo balloon mitral valvuloplasty (BMV) and successfully deserved good result.

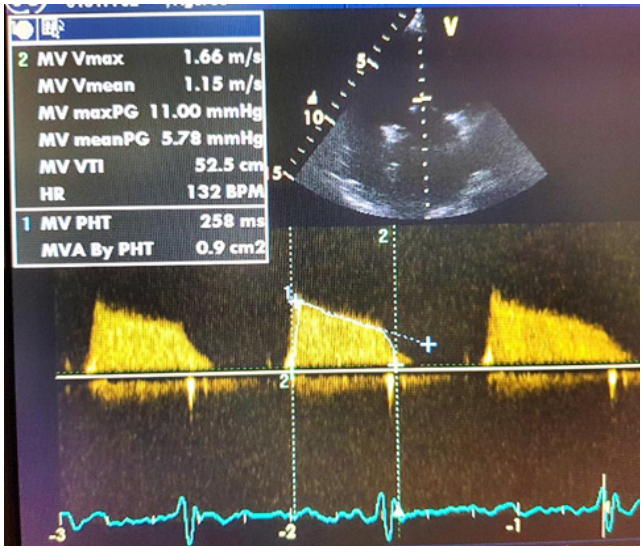

Figure 5. Showing the measurement of mitral valve area and mitral valve gradient

Discussion

Valvular heart disease is associated with a high risk of thromboembolic events.[9] The coexistence of atrial fibrillation and rheumatic mitral stenosis is associated with a higher risk of thromboembolism.[10] The presence of left atrial appendage (LAA) thrombi is a common finding in rheumatic mitral stenosis.[11] The majority of embolisms associated with atrial fibrillation are from the LAA.[12] This LAA has an anatomic structure very favorable for thrombus formation in patients with AF, who often experience limited contraction and stagnant blood flow. In fact, a review of published reports reveals that 90% of cardiothrombic events in patients with AF originate from the LA/LAA.[13] Patient in this case presented with mitral stenosis which never experienced any complaints and had been complicating atrial fibrillation that forming LA thrombus and eventually had an acute stroke.

Thrombus formation occurs along a pathogenesis continuum that starts with SEC or "smoke" formation (erythrocyte rouleaux formation indicative of blood stasis), progresses to sludge formation (very dense smoke) and ends with complete thrombus formation.[14] Persistent SEC in the left atrium on TEE has been associated with later thrombus formation and systemic embolization. Sludge has an echocardiographic appearance that is more viscid than smoke but less dense than thrombus.[15] The anatomic structure of the LAA and acquired enlargement and stretch of the left atrium or LAA in valvular and nonvalvular heart disease provide the milieu for blood stasis. Microscopic endocardial changes in the LAA have been reported in atrial fibrillation as compared with sinus rhythm and mitral stenosis as compared with mitral regurgitation. Edema, fibrinous transformation, and endothelial denudation have been described in the LA tissue in patients with atrial fibrillation and thromboembolism.[16] Rheumatic valve diseases are an important cause of morbidity and mortality, particularly in developing and undeveloped countries.[17]. The slowdown of blood flow and stasis in

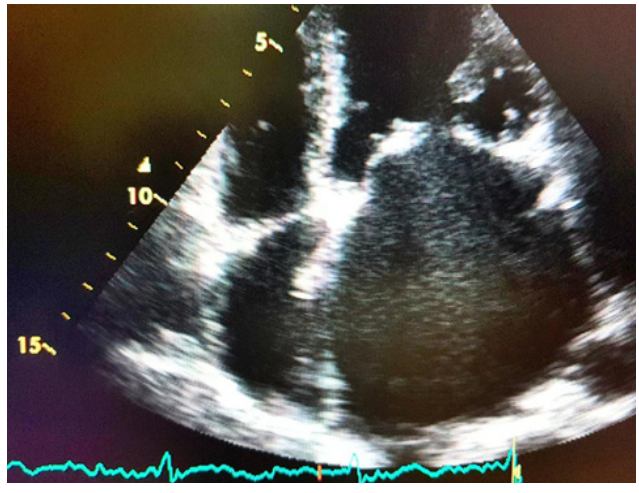

Figure 5. Showing the measurement of mitral valve area and mitral valve gradient

the left atrium associated with rheumatic mitral valve stenosis (RMVS) causes the formation of thrombus.[18] The resulting thrombus joins the systemic circulation from the left atrium and causes embolic complications, the most serious being in the cerebrovascular system. However, it is not possible to explain the development of left atrial (LA) thrombus in patients with MS, and the major embolic events seen in around 20% of these with only valvular obstruction. Rheumatic valve disease is an autoimmune inflammatory process triggered by group A streptococcal infection. The inflammatory reaction continues subclinically and can lead to the progression of valvular damage.[19.20.21] In addition to LA stasis, inflammation, oxidative stress, platelet size, and an increase in activation have been found to be associated with thrombus formation.[22.23] In this case, the patient appeared with acute ischemic stroke due to cardiac emboli which is presumed to be caused by atrial fibrillation and rheumatic mitral stenosis.

Ercan et al. reported a huge left atrial appendage thrombus in a patient with atrial fibrillation which was successfully treated with the combination of acetylsalicylic acid, UFH and tirofiban.[17] Musa Cakici et al reported a case of giant left atrial appendage thrombus due to atrial fibrillation which was successfully treated with the combination of acetylsalicylic acid, UFH, tirofiban and warfarin. The setting of their patient was heart failure and low ejection fraction (30%) with atrial fibrillation. Though there is no consensus on how to treat a giant thrombus with AF in guidelines, [23] but our patient was successfully treated with the combination of UFH and warfarin. The basic consideration of administrating unfractionated heparin in this case regarding the advantages of UFH compared with Low Molecular Weight Heparin (LMWH) are that the anticoagulant effect can be promptly discontinued by stopping the intravenous infusion and it has a wider spectrum of antithrombotic activity.3 On the other hand, ischemic stroke can be transformed to become hemorrhagic especially after thrombolytic therapy. The incidence of spontaneous hemorrhagic transformation (HT) ranges from 38% to 71% in autopsy studies and from 13% to 43% in CT studies, whereas the incidence of symptomatic HT is from 0.6% to 20%.[24,25] Our patient in this case had an acute stroke which was triggered by atrial fibrillation and was administered with UFH infusion without any signs of hemorrhagic stroke. The aPTT monitoring showed that the target level was achieved.

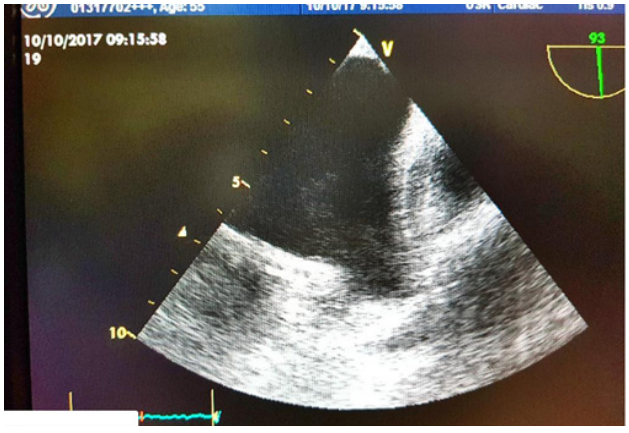

Figure 7. No thrombus found at LAA instead of SEC after the administration of unfractionated heparin

Glycoprotein IIb/ IIIa receptor blockers may be considered as an alternative therapy for giant thrombus in LA or LAA and have been used during percutaneous coronary intervention with a lower rate of bleeding and there are two reports on the successful use of these agents in patients with mechanical valve thrombosis. Additionally, Yuce et.al reported that tirofiban was successfully used for the treatment of atrial septal defect occluder device thrombus in a patient with heart failure.[26,27] However, there is no sufficient evidence for glycoprotein IIb/ IIIa inhibitors in these conditions. Our patient was administered with UFH and warfarin that showed good result; thrombus was completely lysis and the patient was free from the signs of stroke and had been cancelled from the surgical management for her LA thrombus.

Yuechun Li et al has reported a case of a resolution of massive left atrial appendage thrombi with rivaroxaban before balloon mitral commissurotomy in severe mitral stenosis due to intolerable use of warfarin in their patient.[9] However current guidelines include treatment with vitamin K antagonist therapy such as warfarin to dissolve LAA thrombus for patients with valvular atrial fibrillation. However, the use of vitamin K antagonist is limited because of frequent dose adjustment, slow onset of action, and monitoring of coagulation status.[23] Therefore in our case, UFH was administered prior to warfarin to enhance the efficacy in the resolution of the LA thrombus.

Conclusion

This is a case of a patient presenting acute ischemic stroke with atrial fibrillation and severe mitral stenosis. Bed side transthoracal echocardiography (TTE) showed mobile left atrial thrombus which was resolved with the combination treatment of unfractionated heparin and warfarin and the patient showed speedy recovery and eventually underwent BMV with satisfactory result.

Conflict of interest

The authors declared no conflict of interest

List of Abbreviations

AF : Atrial Fibrillation
APTT : Activated plasma thromboplastin time
BMV : Balloon mitral valvuloplasty
CTR : Cardiothorasic ratio
INR : International normalized ratio
LA : Left atrium
LAA : Left atrial appendage
LASEC : Left atrial spontaneous echo contrast
LMWH : Low Molecular Weight heparin
LVEF : Left Ventricle ejection fraction
MS : Mitral stenosis
NCC : Non coronary cusp
NOACs : Novel oral anticoagulants
NYHA : New York Heart Association
PT : Prothrombin time
RAD : Right axis deviation
RCC : Right coronary cusp
RVH : Right ventricle hypertrophy
SEC : Spontaneous echo contrast
TAPSE : Tricuspid annular plain systolic excursion
TEE: Transesophageal echocardiography
HT : Hemorrhagic transformation
TTE : Transthoracal echocardiography
UFH : Unfractionated heparin
VKA : Vitamin K antagonist

References

1. Otto CM . Cardiac Masses and Potential Cardiac Source of Embolus. In Otto CM (ed): Textbook of Clinical Echocardiography, 5th ed. Philadelphia :Elsevier Saunders, 2013, pp 395-414.
2. Tomohiro K, Yutaka M, Teiji Y, Yoshikazu U, Tetsuhito F. Risk Factors for Left Atrial Thrombus from Transesophageal Findings in Ischemic Stroke Patients. Fukushima J. Med. Sci.2014 : 2 (60): 154-158
3. Keith A, A. Fox, Harvey W, Jessica JS, Bernard JG, et al. In Lionel H. Opie (ed): Drugs For The Heart. 7th Ed. Philadelphia :Elsevier Saunders, 2005, pp 293-333
4. Junji T, Hiroshi Y, Takuya O, Kazunori T , Kazuyuki N. Dissolution of the Left Atrial Appendage Thrombus with Rivaroxaban Therapy. Cerebrovasc Dis 2013;36:322–323
5. Luigi DB. Use of Direct Oral Anticoagulant in Patients with Atrial Fibrillation and Valvular Heart Disease. J Am Heart Assoc 2016 :5: e 002776
6. Patel P, Pandya J, Goldberg M. NOACs vs. Warfarin for Stroke Prevention in Nonvalvular Atrial Fibrillation. Cureus. 2017. 9(6): e1395.
7. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-429.
8. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123:e269-367.
9. Yuechun L, Jiafeng L, Chen Peng. Resolution of massive left atrial appendage thrombi with rivaroxaban before balloon mitral commissurotomy in severe mitral stenosis A case report and literature review. Medicine.2016: 95:49 :1-4
10. Petty GW, Khandheria BK, Whisnant JP, et al. Predictors of cerebrovascular events and death among patients with valvular heart disease: a population-based study. Stroke 2000;31:2628– 35.
11. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation

(ARISTOTLE) trial. Circulation 2015;132:624–32.
12. Silaruks S, Thinkhamrop B, Kiatchoosakun S, et al. Resolution of left atrial thrombus after 6 months of anticoagulation in candidates for percutaneous transvenous mitralcommissurotomy. Ann Intern Med 2004;140:101–5.
13. Musa Ç, Mustafa C, Arif S , Mustafa P. Giant left atrial appandage thrombus due to atrial fibrillation: successful treatment with warfarin. Platelets, 2014; 25(4): 303–304
14. Lowe BS, Kusunose K, Motoki H, Varr B, Shrestha K, Whitman C, et al. Prognostic significance of left atrial appendage "sludge" in patients with atrial fibrillation: a new transesophageal echocardiographic thromboembolic risk factor. J Am Soc Echocardiogr 2014;27:1176-83.
15. Hajjiri M, Bernstein S, Saric M, Benenstein R, Aizer A, Dym G, et al. Atrial fibrillation ablation in patients with known sludge in the left atrial appendage. J Interv Card Electrophysiol 2014;40:147-51.
16. Masawa N, Yoshida Y, Yamada T, Joshita T, Ooneda G. Diagnosis of cardiac thrombosis in patients with atrial fibrillation in the absence of macroscopically visible thrombi. Virchows Arch A Pathol Anat Histopathol 1993;422:67-71
17. Ercan S, Sari I, Ozer O, Yuce M, Davutoglu V. Huge left atrial appendage thrombus in a patient with atrial fibrillation: Successful treatment with tirofiban. Platelets. 2013;24(4):333– 334.
18. Stollerman GH. Rheumatic fever. Lancet 1997; 349: 935-42.
19. Fleming HA, Bailey SM. Mitral valve disease, systemic embolism and anticoagulants. Postgrad Med J 1971; 47: 599-604.
20. Golbaşı Z, Ucar O, Keleş T, Şahin A, Cağlı K, Camsarı A, et al. Increased levels of high sensitive C-reactive protein in patients with chronic rheumatic valve disease: evidence of ongoing inflammation. Eur J Heart Fail 2002; 4: 593-5.
21. Chiu-Braga YY, Hayashi SY, Schafranski M, Messias-Reason IJ. Further evidence of inflammation in chronic rheumatic valve disease (CRVD): high levels of advanced oxidation protein products (AOPP) and high sensitive C-reactive protein (hs-CRP). Int J Cardio 2006; 109: 275-6.
22. Akpek M, Kaya MG, Yarlıoglues M, Doğdu O, Ardic I, Şahin O, et al. Relationship between platelet indices and spontaneous echocontrast in patients with mitral stenosis. Eur J Echocardiogr 2011; 12: 865-70.
23. Yuce M, Cakıcı M, Davutoğlu V, Ozer O, Sarı I, Ercan S, et al. Relationship between mean platelet volume and atrial thrombus in patients with atrial fibrillation. Blood Coagul Fibrinolysis 2010; 21: 722-5.
24. Jie Z, Yi Y, Huijie S, Yingqi X. Hemorrhagic transformation after cerebral infarction: current concepts and challenges. Ann Transl Med 2014;2(8):81
25. Conway DS, Buggins P, Hughes E, Lip GY. Relationship of interleukin- 6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation. J Am Coll Cardiol 2004; 43: 2075-82.
26. Jaillard A, Cornu C, Durieux A, et al. Hemorrhagic transformation in acute ischemic stroke. The MAST-E study. MAST-E Group. Stroke 1999;30:1326-32.
27. Yuce M, Davutoglu V, Sari I, Cakici M, Ercan S. Complete thrombus resolution with tirofiban in obstructive mechanical prosthetic mitral valve thrombosis. Platelets. 2010;21(5):386–388.