

Left atrial thrombosis in an anticoagulated patient after bioprosthetic valve replacement: Report of a case

Gian Marco Rosa, Antonello Parodi, Ulrico Dorigi, Federico Carbone, François Mach, Alessandra Quercioli, Fabrizio Montecucco, Nicolas Vuilleumier, Manrico Balbi, Claudio Brunelli

Gian Marco Rosa, Antonello Parodi, Ulrico Dorigi, Manrico Balbi, Claudio Brunelli, Clinic of Cardiovascular Diseases, Internal Medicine Department, San Martino Hospital and University of Genoa, 16143 Genoa, Italy

Federico Carbone, François Mach, Alessandra Quercioli, Fabrizio Montecucco, Division of Cardiology, Department of Internal Medicine, Foundation for Medical researches, University of Geneva, 1211 Geneva, Switzerland

Fabrizio Montecucco, the First Medical Clinic, Laboratory of Phagocyte Physiopathology and Inflammation, Department of Internal Medicine, University of Genoa, 16143 Genoa, Italy

Nicolas Vuilleumier, Division of Laboratory Medicine, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, 1211 Geneva, Switzerland

Author contributions: Rosa GM, Balbi M and Brunelli C designed the report; Parodi A and Dorigi U collected the patient's clinical data; Rosa GM, Carbone F, Mach F, Quercioli A, Montecucco F and Vuilleumier N analyzed the data and wrote the paper.

Supported by Swiss National Science Foundation, No. 310030_118245 and No. 32003B_134963/1

Correspondence to: Fabrizio Montecucco, MD, PhD, Division of Cardiology, Department of Internal Medicine, Foundation for Medical Researches, University of Geneva, 6 viale Benedetto XV, 1211 Geneva, Switzerland. fabrizio.montecucco@unige.ch

Telephone: +41-22-3827238 Fax: +41-22-3827245

Received: October 28, 2013 Revised: November 29, 2013

Accepted: December 17, 2013

Published online: January 16, 2014

disease, VKA was re-established with hemodynamic and liver enzymes normalization and atrial thrombus resolution. Caution has to be used when considering fondaparinux as an alternative strategy to VKA in patients with multiple thrombotic risk factors.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Mitral valve; Thrombus; Prosthetic valve; Atrium; Hepatotoxicity

Core tip: Thromboembolism represents an important complication following heart valve replacement. This case report shows that although vitamin K antagonist (VKA) treatment represents the elective therapy in patients with left atrial thrombosis without mitral valve dysfunction, it may not be sufficient to avoid thromboembolism. We also recommend that the discontinuation of VKA during the first three months after mitral valve surgery has to be carefully considered, especially in high thromboembolic risk patients.

Rosa GM, Parodi A, Dorigi U, Carbone F, Mach F, Quercioli A, Montecucco F, Vuilleumier N, Balbi M, Brunelli C. Left atrial thrombosis in an anticoagulated patient after bioprosthetic valve replacement: Report of a case. *World J Clin Cases* 2014; 2(1): 20-23 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v2/i1/20.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v2.i1.20>

Abstract

We present the case of a 74 year old woman suffering from severe mitral valve incompetence and rapid atrial fibrillation. After an appropriate vitamin K antagonist (VKA) therapy, the patient underwent mitral valve replacement by bioprosthesis. Then, the patient was re-hospitalized for jaundice. Suspecting hepatotoxicity, VKA was discontinued and fondaparinux was started. During this treatment, the patient developed a symptomatic atrial thrombus. After exclusion of a hepatic

INTRODUCTION

Thromboembolism represents an important complication following heart valve replacement. The international guidelines on the management of valvular heart disease recommend postoperative anticoagulation therapy (AT)^[1].

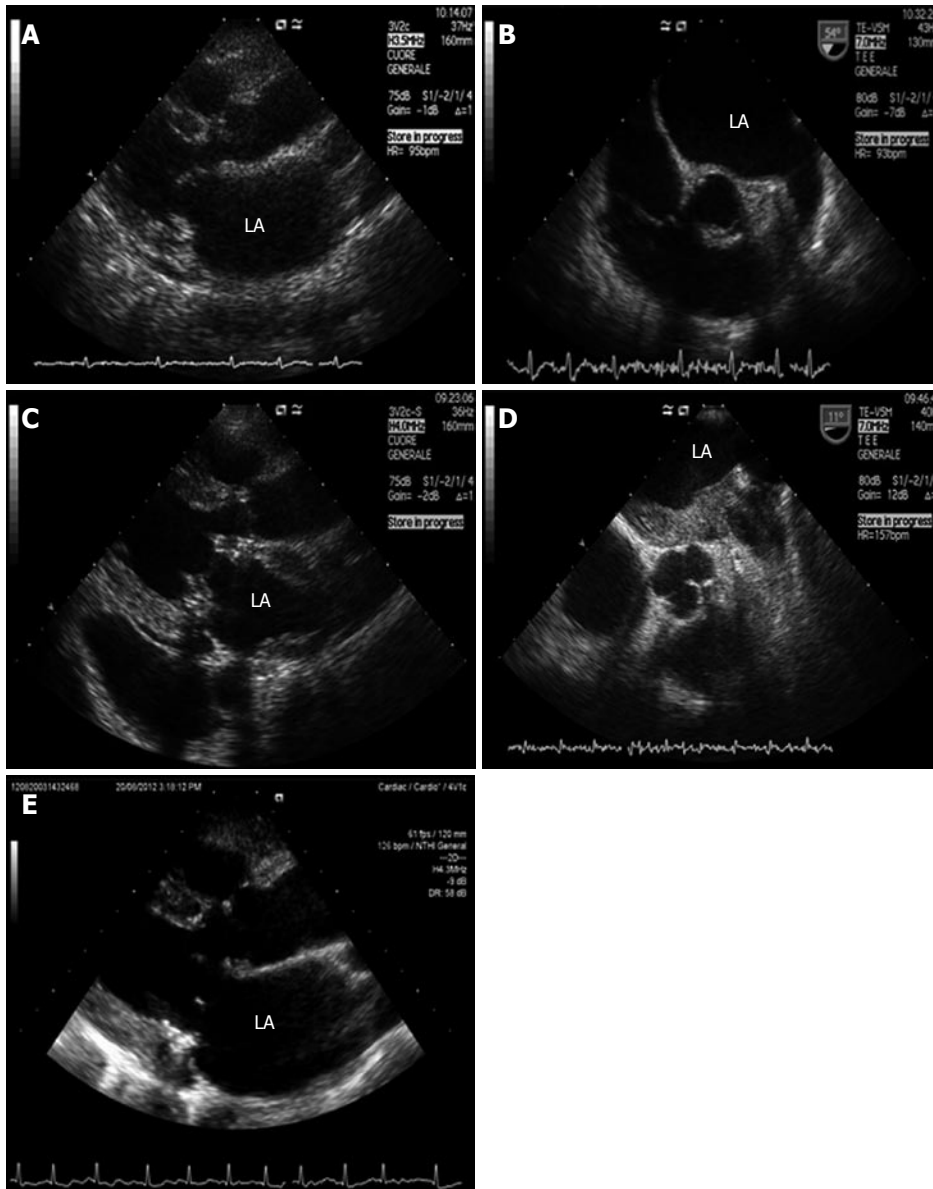


Figure 1 Echocardiographic image. A: Left parasternal long axis transthoracic echocardiography; B: Upper transesophageal views of the aortic valve in short axis; C: Left parasternal long axis transthoracic echocardiography; D: Upper transesophageal views of the aortic valve in short axis; E: Left parasternal long axis transthoracic echocardiography. LA: left atrium.

While mechanical valves require lifelong anticoagulation therapy, bioprosthetic valve (BV) recipients can avoid long-term use. Owing to the higher frequency of thromboemboli in the first 3 mo after BV insertion, three months of AT is recommended for patients not receiving antithrombotic therapy, especially for those who undergo bioprosthetic mitral valve replacement^[2]. However, in the presence of atrial fibrillation (AF), heart failure and impaired LV function (ejection fraction < 30%), AT has to be continued for life.

CASE REPORT

A 74 year old woman with a history of valvular rheumatic disease, acute myocardial infarction, autoimmune thrombocytopenia and paroxysmal atrial fibrillation presented

with palpitations and rapid worsening of dyspnea. She was on antithrombotic therapy with acetylsalicylic acid. EKG showed rapid atrial fibrillation. Transthoracic echocardiography (TTE) demonstrated severe mitral valve incompetence and mild stenosis, enlarged left atrium and right chambers, and severe tricuspid regurgitation (Figure 1A). Appropriate vitamin K antagonist (VKA) therapy was administered.

Transesophageal echocardiography (TEE) showed no thrombus in the left atrium (LA) or in the left atrial appendage (Figure 1B). Since the pharmacological therapy was unable to control the rhythm, the patient was successfully submitted to electrical cardioversion. Five weeks later, the patient underwent mitral valve replacement by Carpentier-Edwards Perimount Magna bioprosthesis (Edwards Lifesciences, Irvine, CA, United States) and tri-

cuspid valve annuloplasty.

In June 2012, the patient was re-admitted because of jaundice and abdominal pain. EKG showed atrial fibrillation. Liver and biliary tract diseases were ruled out despite hyperbilirubinemia and cholestasis indexes (bilirubin was 15.63 mg/dL, γ -glutamyltransferase 1638 U/L, alkaline phosphatase 621 U/L, aspartate aminotransferase 30 U/L, alanine aminotransferase 63 U/L). VKA was discontinued due to suspected hepatotoxicity and fondaparinux was subcutaneously administered (5.0 mg/d). Due to peripheral edema, jugular turgor and hepatomegaly, TTE was repeated over the following days. We found a mass stratified on all the atrial walls (Figure 1C). TEE confirmed that the image was suggestive of thrombus (Figure 1D). Diagnostic workup excluded a thrombophilic state, viral/autoimmune liver disease, cancer or biliary duct pathology. In the first days of July 2012, VKA treatment was re-started and fondaparinux was stopped. In August 2012, the patient showed hemodynamic stability and normalization of the liver function and enzymes, while TTE excluded the presence of a thrombus in the left atrium (LA) (Figure 1E). During 5 mo of follow up, the patient remained asymptomatic.

DISCUSSION

Unlike mechanical heart valves, BV insertion is associated with a very low rate of thrombosis (approximately 0.03% per year)^[3]. After BV implantation, AT is recommended for the first 3 mo and for life only in the presence of atrial fibrillation, heart failure, impaired left ventricular function or history of thromboembolism. Currently, the only oral drugs approved for AT are VKAs.

There is no scientific evidence that the new oral anti-thrombotic agents (*e.g.*, dabigatran, rivaroxaban and apixaban) are effective in these patients. Nevertheless, these drugs could represent a new interesting option because of their elevated safety and efficacy due to their pharmacodynamic profile and the absence of drug-to-drug interactions. The only possible alternatives to VKAs are unfractionated heparin (UFH) and low molecular weight heparins (LMWHs), but they must be administered intravenously or subcutaneously^[1]. Our patient was admitted nearly 40 d after mitral valve surgery when anticoagulation therapy is considered mandatory. Since she was at high thrombotic risk (*e.g.*, age, left ventricular dysfunction, atrial fibrillation, left atrial enlargement with atrial contractile failure), on the basis of the current guidelines, she should have continued AT indefinitely. This treatment strategy is mandatory for the primary prevention of cardioembolic ischemic stroke in patients with cardiac disorders (such as atrial fibrillation). Cardioembolic stroke is considered a high-risk complication and it represents the subtype of ischemic infarct with the highest in-hospital mortality (20%)^[4].

Clinical practice shows that VKA therapy is very effective but long-term administration may be difficult, especially in elderly patients due to the variability in drug

metabolism, drug-drug and drug-food interactions, patient compliance and risk of bleeding events.

The beginning of VKA therapy is burdened by a pro-thrombotic state, so we associated LMWH for few days until reaching the international normalized ratio (INR target), as recommended by international guidelines to avoid thromboembolism.

Our case confirmed this aspect: INR was 4.6 following heart surgery and 1.5 at re-hospitalization after four weeks of therapy at home. Thus, we had to improve anticoagulation by VKA therapy but our concern was related to the increased bilirubin levels and cholestatic indexes suggestive of an acute hepatitis with liver damage.

First of all, we excluded the most frequent causes of acute liver disease. No evidence of viral hepatitis, cholelithiasis and no use of hepatotoxic drugs or toxin ingestion were found. Thus, we theorized that the cause of increased bilirubinemia and cholestatic index levels could be related to the right heart failure with hepatic blood stasis and secondary liver dysfunction.

On the other hand, in accordance with previous reports^[5], we did not continue administering VKAs. Furthermore, we could not administer UFH or LMWH due to the history of immune thrombocytopenia and, moreover, we found some reports of LMWH-induced hepatotoxicity. Thus, we decided to administer fondaparinux. We found little evidence (two experimental models^[6,7] and a case report^[8]) supporting the administration of fondaparinux (7.5 mg once per day) to prevent thrombosis in patients with mechanical heart valves. At that time, we speculated on the potential usefulness of a concomitant antiplatelet therapy (APT). However, we excluded this option considering that there was no evidence of improved efficacy and only an increased hemorrhagic risk.

During an echocardiogram that was carried out to investigate the clinical signs of right heart failure, we found a giant left atrial thrombosis.

These findings, together with the normalization of the hepatobiliary function indexes, suggested to us to discontinue fondaparinux and re-start VKA treatment. Another issue supporting this therapeutic strategy was represented by the concomitant presence of atrial thrombosis without valve dysfunction.

After one month of correct VKA therapy (INR target: 2-3), we not surprisingly found a normally functioning prosthetic valve, accompanied by the resolution of atrial thrombosis. Whether oral anticoagulation may result in the lysis of a thrombus is not clear. Studies carried out for cardioversion in atrial fibrillation have shown that 3-4 wk of warfarin therapy leads to complete resolution of atrial thrombi in 80%-90% of cases without evidence of clinical thromboembolism or residual organized adherent thrombus^[9]. In our patient, this thrombus remodeling may have favored its re-absorption.

Although VKA treatment represents the elective therapy in patients with left atrial thrombosis without mitral valve dysfunction, this case shows that it may be not suit-

able for avoiding thrombogenesis. This case shows that in very high thromboembolic risk patients, VKA therapy never must be discontinued.

This case also suggests that discontinuation of VKAs during the first three months after mitral valve surgery has to be carefully considered, especially in high thromboembolic risk patients. Although we used fondaparinux as an alternative strategy, the efficacy of this drug requires further validation in larger clinical trials.

COMMENTS

Case characteristics

A 74 year old woman with high thromboembolic risk (including atrial fibrillation and previous mitral valve replacement) presented with peripheral edema, jugular turgor and hepatomegaly after withdrawal of the vitamin K antagonist, replaced by fondaparinux.

Clinical diagnosis

Left atrial thrombus and right heart failure.

Differential diagnosis

Left atrial thrombus spontaneous formation or promoted by vitamin K antagonist withdrawal.

Laboratory diagnosis

The metabolic panel that led to the vitamin K antagonist withdrawal showed an increase of bilirubinemia (total bilirubin 15.63/dL), γ -glutamyltransferase (1638 U/L), alkaline phosphatase (621 U/L), aspartate aminotransferase (30 U/L) and alanine aminotransferase (63 U/L).

Imaging diagnosis

Transthoracic echocardiography found a left atrial mass consistent with a thrombus. Transesophageal echocardiography confirmed this insight.

Treatment

The re-initiation of therapy with the vitamin K antagonist led to complete thrombus resolution.

Related reports

Potential liver toxicity induced by the vitamin K antagonist should be considered in clinical practice due to the wide distribution of this drug.

Experiences and lessons

In expectation of new oral antithrombotic agents, the vitamin K antagonist remains the first choice for preventing thrombotic event in high-risk patients. In addition, these patients require a long-term therapy.

Peer review

This article recommends a long-term anticoagulant therapy in high-risk patients and identifies the vitamin K antagonist as the most effective drug.

REFERENCES

- 1 **Vahanian A**, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; **33**: 2451-2496 [PMID: 22922415 DOI: 10.1093/eurheartj/ehs109]
- 2 **Ionescu MI**, Smith DR, Hasan SS, Chidambaram M, Tandon AP. Clinical durability of the pericardial xenograft valve: ten years experience with mitral replacement. *Ann Thorac Surg* 1982; **34**: 265-277 [PMID: 7114945 DOI: 10.1016/S0003-4975(10)62496-4]
- 3 **Grunkemeier GL**, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. *Curr Probl Cardiol* 2000; **25**: 73-154 [PMID: 10709140]
- 4 **Arboix A**, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010; **6**: 150-161 [PMID: 21804774 DOI: 10.2174/157340310791658730]
- 5 **Adler E**, Benjamin SB, Zimmerman HJ. Cholestatic hepatic injury related to warfarin exposure. *Arch Intern Med* 1986; **146**: 1837-1839 [PMID: 3753126 DOI: 10.1001/archinte.1986.0360210235037]
- 6 **Schlitt A**, Buerke M, Hauroeder B, Peetz D, Hundt F, Bickel C, Schaefer I, Meyer J, Rupperecht HJ. Fondaparinux and enoxaparin in comparison to unfractionated heparin in preventing thrombus formation on mechanical heart valves in an ex vivo rabbit model. *Thromb Haemost* 2003; **90**: 245-251 [PMID: 12888871]
- 7 **Schlitt A**, Hamilton K, Maegdefessel L, Dahm M, Theis C, Eichler M, Brockmann O, Steinseifer U, Hauroeder B, Hitzler WE, Rupperecht HJ. Comparison of fondaparinux, low molecular-weight heparin and unfractionated heparin in preventing thrombus formation on mechanical heart valves: results of an in-vitro study. *J Heart Valve Dis* 2006; **15**: 809-814 [PMID: 17152789]
- 8 **Corbett TL**, Elher KS, Garwood CL. Successful use of fondaparinux in a patient with a mechanical heart valve replacement and a history of heparin-induced thrombocytopenia. *J Thromb Thrombolysis* 2010; **30**: 375-377 [PMID: 20571919 DOI: 10.1007/s11239-010-0494-0]
- 9 **Corrado G**, Tadeo G, Beretta S, Tagliagambe LM, Manzillo GF, Spata M, Santarone M. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. *Chest* 1999; **115**: 140-143 [PMID: 9925075 DOI: 10.1378/chest.115.1.140]

P- Reviewers: Arboix A, Amiri M, Biondi-Zoccai G
S- Editor: Qi Y **L- Editor:** Roemmele A **E- Editor:** Wang CH

