CASE REPORT

Left ventricular mural thrombus despite treatment with dabigatran and clopidogrel

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Accepted 5 May 2018

SUMMARY

We describe a case with severe heart failure and moderate aortic stenosis. Due to previous atrial fibrillation and ischaemic heart disease, this patient was treated with both dabigatran and clopidogrel. Despite this, a large mural thrombus was found on echocardiography. The treatment was altered to warfarin, but the thrombus did not resolve during the next eight months.

Guidelines for the use of anticoagulant treatment in left ventricular thrombus are needed. Previously, a few cases presenting resistance to novel oral anticoagulants have been published and cases with thrombus formation due to dabigatran have been described. Our patient showed resistance to both dabigatran and warfarin, and there was no thrombus resolution when changing the treatment to warfarin.

BACKGROUND

The risk of mural thrombus formation in reduced left ventricular function is well known. Studies estimate left ventricular thrombus to occur in 13% of patients with dilated cardiomyopathy during sinus rhythm.¹ According to guidelines, patients with atrial fibrillation should be treated with anticoagulation therapy. However, the role of anticoagulant treatment in patients with heart failure and sinus rhythm is not well established.

Dabigatran, a direct thrombin inhibitor (DTI), is currently approved for prevention of thromboembolic disease in non-valvular atrial fibrillation,^{2,3} and prevention and treatment of deep venous thromboembolism.⁴ Thrombin activates factor V, VIII, XI and XIII, and furthermore converts fibrinogen to fibrin. Dabigatran inhibits thrombin directly by a reversible and competitive binding, while the other novel oral anticoagulants (NOACs) apixaban, rivaroxaban and edoxaban are indirect inhibitors of factor Xa. Heparin inhibits thrombin indirectly by forming a heparin–thrombin–antithrombin complex.⁵ Warfarin is a vitamin K antagonist (VKA) and inhibits the synthesis of factor II, VII, IX and X, plus protein C and S.

The effect of NOAC on prevention of intracardiac thrombus formation and on pre-existing intracardiac thrombus has not been fully explored, and no guidelines are available. Empiric anticoagulant treatment with warfarin and heparin is most often used.^{6,7} However, case reports have been published with resolution of pre-existing thrombi during treatment with dabigatran.^{8–10}

CASE PRESENTATION

An 85-year-old man was referred for echocardiography due to dyspnoea for 3–4 months. There were no complaints of angina. X-ray of the chest showed pulmonary congestion, why his general practitioner had prescribed diuretics.

One year earlier he was admitted to the hospital due to non ST-elevation myocardial infarction, coronary arteriography showed a borderline significant stenosis of the left anterior descending artery (LAD) and no percutaneous coronary intervention was performed. During the hospitalisation, he was furthermore diagnosed with atrial fibrillation and was discharged with dabigatran and clopidogrel, and with a left ventricular ejection fraction (LVEF) of 45%. The clopidogrel treatment was planned to end after 12 months but had mistakenly continued. Dabigatran dose was 110 mg twice daily due to the patient's age and combination therapy with clopidogrel according to guidelines.¹¹

The actual echocardiography revealed LVEF of 20%, a dilated left ventricle and calcification of the aortic valve. Due to low flow and a low gradient, the patient was referred to a dobutamine stress echocardiography to quantify the degree of aortic stenosis. During this examination, a large left ventricular mural thrombus was discovered (figure 1, video 1). By re-evaluation of the previous echocardiography made 5 days earlier, the mural thrombus was visualised in that echocardiography as well. At that time, the patient had been on double anticoagulant treatment with dabigatran (110 mg twice daily) and clopidogrel (75 mg) for >1 year.

INVESTIGATIONS

A coronary arteriography showed unaltered borderline stenosis of the LAD, and no percutaneous coronary intervention was indicated.

The dobutamine stress echocardiography revealed only a moderate aortic stenosis as the valve area increased from 0.7 to 1 cm² with an increase in peak gradient from 10 to 23 mm Hg, and an increase in stroke volume from 23 to 44 mL. The dobutamine stress test ended at 15 µg/kg/min due to an increasing number of ventricular extra systoles.

DIFFERENTIAL DIAGNOSIS

Mural thrombus in the cavity of the heart may also be found in hypereosinophilic endocarditis. This patient did not have abnormal eosinophilic leucocytes at any time of investigation. Therefore, we did not perform a cardiac MRI scan to verify this differential diagnosis.

To cite: Fredgart M, Gill S. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223899

Figure 1 Transthoracic echocardiography showing a large mural thrombus in the left ventricular (LV) chamber prior to warfarin treatment. Arrow indicates mural thrombus. RV, right ventricle.

TREATMENT

After the detection of the thrombus, the patient was admitted to the hospital. Dabigatran and clopidogrel treatment was ended, and bridging with low-molecular-weight heparin was initiated together with warfarin with a target interval for international normalised ratio (INR) between 2 and 3.

The patient was medicated with diuretics, spironolactone and statin, and an ACE inhibitor plus beta-blockers were added for anticoagestive treatment.

OUTCOME AND FOLLOW-UP

Follow-up echocardiography was performed 2, 5 and 7 months after discharge with only a small reduction in mural thrombus size.

Eight months after detecting the mural thrombus, the patient was resubmitted as a result of multiple episodes of syncope, no dyspnoea or angina was reported, but the patient complained of dizziness. Blood pressure was recorded in the emergency room of 81/53 and ECG revealed a bifascicular block. Blood samples showed a troponin I of 2516 ng/L (normal reference value: <14 ng/L), decreasing the following day.

Video 1 Transthoracic echocardiography revealing a large mural thrombus in the left ventricular chamber prior to warfarin treatment.

Figure 2 Transthoracic echocardiography displaying the left ventricular (LV) thrombus after 6 months of warfarin treatment. RV, right ventricle.

The patient reported a weight loss of 20 kg during the last three months. A gastroscopy 2 months prior to the submission showed candidiasis in the oesophagus. Immunoglobulins, M-component and an HIV test were performed, all came out negative. The thrombus in the left ventricular apex, a LVEF of 10%–15% and global hypokinesia especially in the posterior segments was visualised with echography (figure 2).

The patient developed sepsis and circulatory collapse, and passed away a week after the admission. The autopsy showed no signs of malignancy, a severe aortic valve calcification and severe atherosclerosis of the three coronary arteries most prominent on the proximal part of LAD. The heart was hypertrophic (800 g) with dilated ventricles. In the left ventricle, a large (4 cm × 1.5 cm × 1.5 cm) mural thrombus was adherent to the endocardium. Histology of the heart revealed fibrosis from an old infarction and several foci with infiltration of neutrophilic granulocytes and necrotic myocytes indicating a recent infarction.

DISCUSSION

The formation of intracardiac thrombus is well known in patients with atrial fibrillation. More infrequently formation of left ventricular thrombus occurs in patients with myocardial infarction,¹² dilated cardiomyopathy¹ and acute myocarditis.¹³

VKA and NOACs are equally used for prevention of thromboembolic disease in atrial fibrillation. The disadvantages of VKA are frequent measurements of INR, interaction with food containing vitamin K and a narrow therapeutic window; therefore, treatment with NOACs is more and more often used as first drug of choice.

Table 1 List of medications received by the patient when the mural thrombus was first discovered		
Medicine	mg	Dose
Clopidogrel	75	×1
Dabigatran	110	×2
Furosemide	80	×2
Potassium chloride	750	×2
Metoprolol succinate	50	×1
Rosuvastatin	5	×1
Spironolactone	50	×2

Our patient was very compliant with his medication, and none of his other drugs was interacting with dabigatran (table 1). However, he received the lower dose due to a combined treatment with clopidogrel and age >80 years. This lower dose may result in a low and inadequate plasma level of dabigatran. Variation in Dabigatran plasma levels up to fivefold has been described, and this may explain the ineffectiveness of dabigatran in our patient.¹⁴

To our knowledge, there is sparse evidence about dabigatran resistance. A few cases have been published with patients developing thrombus during dabigatran treatment, and in some cases the thrombus was completely dissolved following warfarin initiation. Therefore, thrombus promotion by dabigatran use rather than dabigatran resistance has been hypothesised.^{15–18} Dabigatran inhibits activated protein C and thereby enhances thrombin generation and coagulation. This opposing effect of DTI is not fully understood but could partly explain our findings as it may have promoted thrombus formation.¹⁹ But even though the patient was treated with a DTI, he had additional treatment with clopidogrel, an ADP receptor antagonist that inhibits platelet function.

Whether treatment with one of the other NOACs would have resulted in less thrombus formation might be questioned as these act indirectly due to factor Xa inhibition.

The thrombus formation could also be explained by Virchow's triad—reduced wall motion, local myocardial injury and hypercoagulability/stasis of the blood—the latter due to the presence of aortic stenosis. A dobutamine stress test was performed to assess the degree of aortic stenosis. However, the dobutamine infusion was stopped before obtaining a valve area >1 cm²; therefore, a potential severe aortic stenosis could have been missed.

After a change of anticoagulant therapy to warfarin, the thrombus was not dissolved after 8 months of compliant treatment. Thrombus age could partly explain this since the older the thrombus the less likely is thrombus dissolution in spite of correct anticoagulant treatment. A fresh thrombus mainly consists of blood material, whereas an old thrombus is organised with collagen. Treatment strategy of persistent thrombus is not clear. If the thrombus is old, organised and perhaps even calcified, some experts suggest that anticoagulation can be ended since the risk of embolisation is minimal.²⁰

Patient's perspective

- Although treatment with dabigatran and clopidogrel was received, thrombus formation occurred. Considering the augmented risk of bleeding by double anticoagulant therapy, this increased risk does not give a guarantee against thromboembolic events.

Learning points

- Good compliance is no guarantee for effective treatment with dabigatran.
- Double anticoagulant therapy, although giving an increased risk of bleeding, does not necessarily prevent intracardiac thrombus formation.
- Warfarin treatment may not be sufficient for intracardiac thrombus resolution over a period of 8 months follow-up when treating organised thrombi.
- The most efficient anticoagulant treatment for left ventricular thrombus is still unclear.
- More knowledge and guidelines are needed in the field to advance treatment of left ventricular thrombus.

A comprehensive set of guidelines regarding left ventricular thrombus treatment is needed. Habash *et al* have recently reviewed current literature in this field and concluded that prospective studies are needed to advance treatment of left ventricular thrombus.²⁰

Contributors SG has treated the patient and has planned the writing of a case report. MF has written the case report and has later also treated the patient herself. Acquisition and analysis of data has been performed by SG and MF. SG has found the video and picture displaying the mural thrombus.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- Bakalli A, Georgievska-Ismail L, Koçınaj D, *et al*. Prevalence of left chamber cardiac thrombi in patients with dilated left ventricle at sinus rhythm: the role of transthoracic echocardiography. *J Clin Ultrasound* 2013;41:38–45.
- Kirchhof P, Benussi S, Kotecha D, *et al*. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO). Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology. *European Society of Cardiology* 2016.
- Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
- Hill J, Treasure T. National Clinical Guideline Centre for Acute and Chronic Conditions. Reducing the risk of venous thromboembolism in patients admitted to hospital: summary of NICE guidance. *BMJ* 2010;340:c95.
- Lee CJ, Ansell JE. Direct thrombin inhibitors. *Br J Clin Pharmacol* 2011;72:581–92.
- Selvanayagam JB, Spyrou N, Francis JM, *et al*. Resolution of ventricular thrombus identified by contrast enhanced cardiac MRI. *Int J Cardiovasc Imaging* 2004;20:369–70.
- Tilling L, Becher H. The vanishing vast ventricular thrombus. *Eur J Echocardiogr* 2007;8:67–70.
- Kolekar S, Munjewar C, Sharma S. Dabigatran for left ventricular thrombus. *Indian Heart J* 2015;67:495–6.
- Kaku B. Intra-cardiac thrombus resolution after anti-coagulation therapy with dabigatran in a patient with mid-ventricular obstructive hypertrophic cardiomyopathy: a case report. *J Med Case Rep* 2013;7:238.
- Nagamoto Y, Shiomi T, Matsuura T, *et al*. Resolution of a left ventricular thrombus by the thrombolytic action of dabigatran. *Heart Vessels* 2014;29:560–2.
- Dansk Kardiologisk Selskab. Akut koronar syndrom. 2017. http://nbv.cardio.dk/aks#afs1_6
- Keeley EC, Hillis LD. Left ventricular mural thrombus after acute myocardial infarction. *Clin Cardiol* 1996;19:83–6.
- Kontani M, Takashima S, Okura K, *et al*. Survival after acute necrotizing eosinophilic myocarditis complicating a massive left ventricular mural thrombus: a case report. *J Cardiol* 2007;50:127–33.
- Reilly PA, Lehr T, Haertter S, *et al*. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol* 2014;63:321–8.
- Sargento-Freitas J, Silva F, Pego J, *et al*. Cardioembolic stroke in a patient taking Dabigatran Etexilate: the first case report of clinical and pharmacologic resistance. *J Neurol Sci* 2014;346(1–2):348–9.
- Sharma S, Singh S, Sandhu R, *et al*. Case report series of left atrial thrombus formation in patients on dabigatran therapy. *Am J Ther* 2014;21:e71–4.
- Shah P, Mithawala P, Konlian D, *et al*. Thrombus formation in left atrium on dabigatran therapy. *Case Rep Cardiol* 2015;2015:1–2.
- Adar A, Onalan O, Cakan F. Newly developed left ventricular apical thrombus under dabigatran treatment. *Blood Coagul Fibrinolysis* 2018;29:126–8.
- Fragasso G, Corti A, Loiacono F, *et al*. Oral direct thrombin inhibition: a double-edged sword? *Heart Lung Vessel* 2015;7:191–7.
- Habash F, Vallurupalli S. Challenges in management of left ventricular thrombus. *Ther Adv Cardiovasc Dis* 2017;11:203–13.

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