Hyperthyroidism in severe mitral regurgitation post mechanical mitral valve replacement: the effect on warfarin anticoagulation

Gracia Lilihataa, Charles Saputraa, Dian Yaniartib and Rarsari Soerarsob

A 24-year-old male patient came to the emergency room with melena, gum bleeding and nosebleeds. This patient has a history of mechanical prosthetic mitral valve replacement for severe mitral regurgitation (MR) and consumed warfarin irregularly, but did not come back for regular check-up. Investigations showed greatly increased thyroid function and international normalised ratio (INR) was 15.8. Patients were diagnosed with thyroid storm and bleeding due to prolongation of INR. His hyperthyroid state might have caused increased rate of degradation of vitamin K-dependent clotting factor thereby increased sensitivity to warfarin. Concomitant acute decompensated heart failure, thrombocytopenia and hypoalbuminemia also contributed to his risk of bleeding. Treatment included anti-thyroid therapy as well as warfarin reversal therapy by stopping warfarin, low-dose intravenous vitamin K due to his mechanical prosthetic valve and fresh frozen plasma. In conclusion, hyperthyroidism could increase the response to warfarin so close monitoring is needed to balance the risk of bleeding and thromboembolism.

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Introduction

Lifelong anticoagulation with oral vitamin K antagonists, warfarin is obligatory in patients with mechanical prosthetic valve to prevent thrombosis and thrombo-embolic event [1]. However, warfarin has narrow therapeutic index and requires close monitoring of international normalised ratio (INR). Furthermore, many factors could affect warfarin anticoagulation effect such as thyroid dysfunction. Hyperthyroidism increases catabolism of vitamin K-dependent clotting factor, therefore increases sensitivity to warfarin. In contrast, hypothyroidism decreases response to warfarin [2,3]. Other concomitant factor such as other comorbid, hypoalbuminemia or thrombocytopenia will also increase bleeding tendency. As anti-thyroid therapy started, frequently INR will fall to subtherapeutic level, thus predispose patient to thrombotic risk and add another complexity in the situation. To our knowledge, this is the first case report describing effect of hyperthyroidism on warfarin anticoagulation in complex interaction with other comorbid condition.

Case

A 24-year-old male patient presented to the emergency room (ER) with melena and gum bleeding for 4 days. He also experienced fever accompanied by palpitations, increased appetite, heavy sweating, fatigue and progressive shortness of breath since one week before. Productive cough was also present. Stomach was distended and legs were swollen. Patient denied any history of vomiting blood, headache, projectile vomiting, asymmetric weakness nor loss of consciousness.

The patient has a history of mechanical mitral valve replacement (MVR) on August 2017 for severe degenerative mitral regurgitation (MR). Following the valve replacement surgery, warfarin anticoagulation was initiated but patient experienced extreme prolongation of INR up to 10 and subarachnoid hemorrhage. Because patient was persistently tachycardic at that time, thyroid function was checked and showed that patient was in hyperthyroid state. Warfarin was then stopped, and vitamin K and anti-thyroid therapy with propylthiouracil (PTU) was started. At discharge, warfarin was re-started again as well as PTU, bisoprolol and captopril. However, from 2018 to 2020 patient never came back for follow-up. He continued to take warfarin irregularly by buying it at local pharmacy. Other anti-thyroid and anti-failure medication was discontinued by the patient. He admitted that he did not understand the importance of the medication and regular follow-up.

Physical examination at ER showed the patient was agitated, heart rate was 120 × bpm and temperature was 38.2°C. Proptosis, fine tremors and diffuse goiter sized 5 × 5 cm in the anterior neck were noted. Jugular vein was distended; rales on both the lungs, ascites and edema on lower extremities were present. On cardiac auscultation, mechanical second heart sound was present. The
electrocardiography showed sinus tachycardia, incomplete right bundle branch block pattern and left ventricle hypertrophy (LVH). Significant laboratory test results were hemoglobin 10.6 g/dl, platelets 129,000/μl, INR 15.8, albumin 2.8 g/dl, total bilirubin 4 mg/dl, direct bilirubin 3.38 mg/dl, indirect bilirubin 1.31 mg/dl, TSH was suppressed to 0.116 μU/ml (ref 0.27–4.2 μU/ml) and FT4 was elevated to >7.77 mg/dl (ref 0.93–1.7 mg/dl). Chest radiograph showed cardiomegaly, flattening of the heart’s waist, congestion, as well as infiltrates in right perihilar. Burch-Wartofsky Scale Index in this patient was 75, which was very suggestive of thyroid storm.

The patient was diagnosed with gastrointestinal bleeding caused by prolonged INR, acute decompensated heart failure caused by thyroid storm in severe MR after mechanical-prosthetic MVR, anemia, thrombocytopenia, hypoalbuminemia and community-acquired pneumonia. In the ER, patient was given injection of vitamin K 1 mg IV, transfusion of fresh frozen plasma (FFP), along with PTU, dexamethasone, propranolol, pantoprazole, sucrafate, empirical antibiotic and diuretic.

On the second day of admission, INR was down to 1.88 and no more signs of bleeding were noted. On seventh day of admission, fecal occult blood test was negative, so warfarin was resumed again. However, thrombocyte level continues to decline. Full diagnostic transthoracic echocardiography showed eccentric LVH, left ventricle (LV) ejection fraction 64% and TAPSE 1.7 cm, prosthetic mitral valve gradient was 8–12 mmHg, MVA VTI 1.9 cm² and minimal pericardial effusion was present in posterior LV. No masses/thrombus was noted.

Toward the end of hospitalization, liver function and thrombocyte count returned to normal level. Repeat thyroid function showed TSH was still low but FT4 already decreased (Table 1) so PTU dose was lowered to 100 mg bid. Albumin level remained low. However, 24-h microalbuminuria examination was negative and renal function was normal. On 14th day of hospitalization, patient was discharged with warfarin 2 mg OD, along with PTU 100 mg bid, ramipril, bisoprolol and furosemide. One week after discharge, patient came back for follow up visit and INR was 1.2. Warfarin dose was maintained and patient was asked to check thyroid function monthly.

### Discussion
Hyperthyroidism shifts hemostasis to procoagulant and prothrombotic state by increasing the production of clotting factors, von Willebrand factor and plasminogen activator inhibitor-1. At the same time, hyperthyroidism also increases the degradation of vitamin K-dependent clotting factors [2,3]. Warfarin works by inhibiting vitamin K epoxide reductase complex in the liver, causing the depletion of reduced form of vitamin K needed for gamma-carboxylation of vitamin K-dependent coagulation factors, including factors II, VII, IX and X. As a result, the production and function of these factors are inhibited [4]. When hyperthyroid patient receives warfarin, the production of vitamin K-dependent coagulation factors is inhibited, while the degradation rate is increased. In addition, thyroid hormone increases the affinity of warfarin for its receptors in the liver thereby further suppressing the production of vitamin K-dependent clotting factors [3,5]. Therefore, patients with hyperthyroidism will have excessive anticoagulation response to warfarin.

Thrombocytopenia in our patient might also be caused by hyperthyroidism and contributed to his risk of bleeding. Hyperthyroidism is known to shorten the lifespan of platelets and increase the phagocytic activity of the reticuloendothelial system. In the case of autoimmune hyperthyroidism, it is thought that some antibodies exist against both platelets and thyroid gland [6]. The thrombocyte count returned to normal level after antithyroid therapy was started and patient became euthyroid.

Hypoalbuminemia was another important contributing factor in this patient’s risk of bleeding. Hypoalbuminemia causes increased biologically active free fraction of warfarin and exaggerated anticoagulation response [7,8]. Hypoalbuminemia in our patient could be caused by multiple factors: (1) direct effect of thyrotoxicosis, (2) secondary to congestive heart failure (CHF) or (3)

### Table 1  Summaries of laboratories result during hospitalization and follow-up

<table>
<thead>
<tr>
<th>Item</th>
<th>Inpatient</th>
<th>OPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>12/2</td>
<td>2/3</td>
</tr>
<tr>
<td>Throm (μl)</td>
<td>129,000</td>
<td>11.1</td>
</tr>
<tr>
<td>TSH (ref 0.27–4.2 μU/ml)</td>
<td>0.116</td>
<td>0.019</td>
</tr>
<tr>
<td>FT4 (ref 0.93–1.7 mg/dl)</td>
<td>&gt;7.77</td>
<td>0.35</td>
</tr>
<tr>
<td>INR</td>
<td>15.83</td>
<td>1.2</td>
</tr>
<tr>
<td>SGOT (0–41 U/l)</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>SGPT (0–50 U/l)</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>Albumin (ref 3.5–5.2 g/dl)</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Total bilirubin (0–1.4 mg/dl)</td>
<td>4.69</td>
<td>4.69</td>
</tr>
<tr>
<td>Direct bilirubin (0–0.3 mg/dl)</td>
<td>3.38</td>
<td>3.38</td>
</tr>
<tr>
<td>Indirect bilirubin (0–0.75 mg/dl)</td>
<td>1.31</td>
<td>1.31</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; INR, international normalised ratio; OPD, outpatient department; Throm, thrombocyte.
reduced intake. Hyperthyroidism increases basal metabolism thereby increases energy burning, lipolysis and proteolysis. Protein breakdown is increased while protein synthesis remains stable causing a decrease in body protein levels [9]. Hyperthermia also can cause direct impairment of liver function and interfere with its ability to synthesize albumin.

Patients with CHF experience fluid overload and congestion in the liver, which could directly or indirectly result in unstable INR [10,11]. In ‘theory of oxygen limitation’, liver congestion disturbs oxygen diffusion to the liver thereby reducing the ability of warfarin oxidative metabolism. Indirectly, liver congestion also decreases clotting factor and albumin synthesis ability. Gastrointestinal congestion can also impair protein and vitamin K absorption [5].

Our patient’s INR returned to normal value the next day after stopping warfarin, anti-thyroid was started, and FFP transfusion and vitamin K injection were given (Table 1). In fact, during hospitalization and follow-up, patient’s INR became subtherapeutic. The warfarin dose should have been increased; however, the cardiologist maintained previous warfarin dose because patient had poor compliance and limited access for regular blood checking so it would be wiser to give this patient a very good education before increasing the dose.

Similar report by Busenbark et al. followed a patient with hyperthyroidism, who was started on methimazole concomitantly with warfarin for atrial fibrillation. As patient became hypothyroid on treatment, the INR target was not achieved and the warfarin dose had to be increased to reach the desired INR. When methimazole was stopped and the patient returned to hyperthyroidism, the INR became supratherapeutic [12]. Another study by Howard-Thompson et al. followed a patient with Grave’s disease, who received warfarin for new onset atrial fibrillation but stabilization of INR and warfarin dose was difficult to achieve during concomitant methimazole therapy. After the patient underwent radioactive iodine ablation and became euthyroid, the dose of warfarin and INR stabilized [3]. Whether the difficulty in stabilizing INR and warfarin dose is caused by direct drug-to-drug interaction between antithyroid drug and warfarin is still unclear. However, it is thought that changes in thyroid function due to anti-thyroid treatment are the actual cause of variability in the response to warfarin [3]. Definitive therapy for hyperthyroid with surgery or ablation must be considered in patients with difficulty stabilizing INR or poor compliance to medication. For acute warfarin reversal therapy, treatment includes stopping warfarin, vitamin K and FFP or prothrombin complex concentrate if available. However, in patient with mechanical prosthetic valve, low dose of vitamin K is recommended instead of higher dose to avoid risk of hypercoagulation and thrombosis [1]. High dose of vitamin K could also lead to prolonged increase of vitamin K plasma levels, which may hinder re-anticoagulation [13].

Conclusion

Hyperthyroidism might have caused excessive response to warfarin because it increases vitamin K-dependent clotting factors degradation and at the same time suppresses its synthesis. The risk of bleeding in this patient was enhanced by thyrotoxicosis-induced hypoalbuminemia, thrombocytopenia and CHF. Careful consideration and frequent monitoring is needed to balance the risk of future bleeding and thrombotic complication.

Acknowledgements

Informed consent has been obtained from the patient to publish this case report.

Conflicts of interest

There are no conflicts of interest.

References

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