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Thyroidectomy in Mechanical Circulatory Support - A Salvage Treatment for Thyrotoxicosis-Induced Cardiogenic Shock: Case Series

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Abstract

Amiodarone is frequently used to treat arrhythmias in patients supported with left ventricular assist devices. Long term amiodarone use can cause hyperthyroidism ultimately leading to cardiomyopathy and sometimes thyrotoxicosis-induced cardiogenic shock (CS). We describe two cases of thyrotoxicosis-induced CS rescued by successful thyroidectomy under mechanical circulatory support (MCS) – one with a Heartmate III (Abbott Laboratories) and another supported with veno-arterial extracorporeal membrane oxygenation (V-A ECMO). In refractory CS, the initiation of V-A ECMO as a bridge to recovery is critical. In thyrotoxicosis-induced CS that is refractory to medical therapy requiring MCS, thyroidectomy is feasible, and a growing body of evidence suggests that it is safe.

Background

Left ventricular assist devices (LVADs) are being increasingly utilized as destination therapy, a bridge to candidacy, or a bridge to transplantation for patients with end stage heart failure (HF).[1] While ventricular arrhythmias are common in patients supported by LVADs, they are also well-tolerated.[2] Amiodarone is an effective first line agent to treat ventricular arrhythmias post-LVAD implantation. However, chronic treatment with amiodarone can lead to hyperthyroidism or hypothyroidism.[3] Thyrotoxic cardiomyopathy (TCM) and thyrotoxicosis-induced cardiogenic shock (CS) are uncommon but critical complications of hyperthyroidism. Thyrotoxicosis-induced CS is a life-threatening event with a very high mortality.[4,5] Therefore, patients in CS may benefit from veno-arterial extracorporeal membrane oxygenation (V-A ECMO) support. Although thyroidectomy is well-established in cases of refractory thyrotoxicosis, the safety and efficacy of thyroidectomy in patients with mechanical circulatory support (MCS) is uncertain. We describe two cases of thyrotoxicosis-induced CS. We briefly discuss the pathophysiology of thyrotoxicosis-induced CS, unsuccessful medical therapy, and successful thyroidectomy under MCS leading to the resolution of thyrotoxicosis, refractory atrial fibrillation (AF), and CS in both cases.

Case Report

Case One

A 41-year-old male with a history of morbid obesity, obstructive sleep apnea, recurrent pulmonary embolism (PE), and end-stage HF with reduced ejection fraction (EF) due to nonischemic dilated cardiomyopathy presented to our hospital. The patient's history included placement of a biventricular implantable cardioverter-defibrillator followed by a diagnosis of paroxysmal AF two years later. Amiodarone was prescribed to treat the AF. Eleven months later the patient was hospitalized for a PE and was receiving apixaban. During this hospitalization, the patient was diagnosed with hypothyroidism and started on low dose levothyroxine at discharge. His thyroid stimulating hormone (TSH) levels were continuously checked (**Table 1**). One month after the PE hospitalization, the patient received a HeartMate III LVAD (Abbott Laboratories) as a bridge to transplantation. The patient's anticoagulation and antiplatelet regimen were aspirin (81 mg daily) and warfarin with an international normalized ratio (INR) goal between 2 and 3. Eight months after LVAD implantation, the patient's post-operative course was complicated by a chronic *Enterobacter* driveline infection; doxycycline was prescribed.

Two years after his LVAD implantation (37 months after the initiation of amiodarone), he presented to the hospital in severe respiratory distress. Over the previous 2 days, the patient suffered nausea, vomiting, diarrhea, and intermittent fevers. He was found to be in AF with rapid ventricular response (RVR) and was emergently intubated. The patient was in CS, and his initial vitals and laboratory results are presented in **Table 2**. Lactate dehydrogenase (LDH) was elevated

Table 1. Thyroid function tests for Case 1. The patient began receiving amiodarone for atrial fibrillation. He was diagnosed with hypothyroidism 11 months later and his levels were tracked from that point. **indicates the time of the hospitalization for thyroidectomy*.

Months after the initiation of amiodarone	*11*	*13*	*17*	*33*	*37**	*38*
Thyroid stimulating hormone (mcU/mL)	7.5	3.4	2.9	2.0	<0.01	3.1
Free thyroxine 4 (ng/dL)	1.0	N/A	N/A	N/A	5.4	1.2

Table 2. Vital signs and laboratory results for Case 1. Upon presentation to our hospital, the patient was in cardiogenic shock and atrial fibrillation with rapid ventricular response. *HR – heart rate; MAP – mean arterial pressure; LDH – lactate dehydrogenase; INR – international normalized ratio; AST/ALT – aspartate transaminase/alanine transaminase; Hgb-hemoglobin*

Variable	*HR*	*MAP*	*Lactic acid*	*LDH*	*INR*	*AST/ ALT*	*Hapto-globin*	*Plasma free Hgb*
Result	180 beats/ min	45 mmHg	7.3 mmol/ L	1508 Units/ L	8.4	134/ 68	< 6 mg/dl	2 mg/dl

to 1508 from a baseline of 500 units/L. The haptoglobin was less than 6 mg/dl, which is well below the normal range of 30-200 mg/dl.

The LVAD pump speed was increased from 6000 rpm to 6800 rpm to augment cardiac output with shock. Given the presence of elevated markers of hemolysis and CS, there was an initial concern for possible pump thrombosis or LVAD outflow tract obstruction. However, LVAD pump parameters were unchanged upon review (speed: 6800 rpm, flow: 2.7 L/min, power: 5.4 W, pulse index: 2.4). A computed tomography angiography of the chest showed mild peripheral circumferential low attenuation of the outflow graft, which was likely to be mild laminar thrombosis. Thus, no thrombolytics were used. Both the LDH and INR normalized without any intervention. Despite LVAD support, left ventricular (LV) systolic function remained severely depressed with an EF of 10%, and AF was refractory. Despite multiple cardioversions, amiodarone, and digoxin loading, the patient eventually required atrioventricular pacing due to arrhythmia-related hypotension. He required pressor support, multiple reintubations, and suffered recurrent fevers even though the infectious work up was negative.

A chest x-ray showed a pulmonary vascular congestion in keeping with volume overload, and his driveline culture was positive for known *Enterobacter*. He was started on empiric antibiotics. TSH was undetectable and reflex thyroxine (T4) was elevated (**Table 1**). At that time, thyrotoxicosis was felt to be causative of his refractory fever, diarrhea, AF, and CS. Endocrinology was consulted. Amiodarone was stopped while methimazole, steroids, and propranolol were started for thyroid storm due to suspected amiodarone-induced thyroiditis (AIT). However, surgery was a more definitive treatment for this patient due to his poor response to medical therapy. A total thyroidectomy was successful without any post-operative complications. Thyroid tissue pathology showed disrupted follicles with desquamated vacuolated epithelial cells, intra- and perifollicular aggregates of foamy macrophages, and follicles with flattened or apoptotic follicular cells consistent with AIT type 2. Post-thyroidectomy, his EF improved to 25%, and his sinus rhythm was successfully restored. The patient was discharged 5 days later in his usual state of health.

Case Two

A 51-year-old female with hyperthyroidism presented to the emergency department in AF with RVR (heart rate was 160 – 190 beats/min). She had a history of worsening dyspnea (one month), diarrhea (one week), and fevers (one week). She was not taking any medications for the hyperthyroidism.

TSH was undetectable and free T4 was elevated (**Table 3**). Both diltiazem and esmolol were given, but neither successfully controlled the heart rate.

Table 3. Thyroid function tests for Case 2. The patient's thyroid function was monitored over the course of her hospitalization. A subtotal thyroidectomy was done on Day 9.

Hospitalization	*Day 0 (Admission)*	*Day 6*	*Day 41*	*Day 59*
Thyroid stimulating hormone (mcU/mL)	< 0.010	0.059	< 0.010	< 0.010
Total thyroxine 4 (mCg/dL)	28.9	17.4		9.6
Free thyroxine 4 (ng/dL)	5.2	2.1	0.7	1.1
Total thyroxine 3 (ng/dL)	227	194		
Free thyroxine 3 (pg/mL	17.4		<10.0	1.5

The patient was transferred to our tertiary center. Because she was in CS and suffering a thyroid storm, she was sedated, intubated, and initially treated with methimazole, propranolol, hydrocortisone, cholestyramine, and Lugol's solution.

Both pressors and inotropic support were used to treat her hypotension. Due to her hemodynamic instability and sustained AF, a transesophageal echocardiogram was performed and showed *de novo* severely depressed LV function with an EF of 10% and no left atrial appendage thrombus. She underwent multiple cardioversions. An amiodarone infusion was used first, and she was eventually transitioned to sotalol. The patient's condition progressively deteriorated despite aggressive hemodynamic support with high doses of inotropic and vasopressor agents. Despite these interventions, episodes of AF continued unabated.

She ultimately required plasmapheresis for her thyroid storm as her liver function values began to increase while on methimazole, likely secondary to CS. V-A ECMO was then initiated for worsening CS, lactic acidosis, increasing pressor requirements, and multisystem organ failure. She also needed continuous veno-venous hemofiltration for hyperammonemia and anuria. Surgery was consulted for further management as she did not tolerate methimazole, and plasmapheresis was not a viable long-term solution.

The risk of morbidity and mortality were deemed to be very high regardless of whether a thyroidectomy was done. After discussion with the patient's family, an urgent total thyroidectomy with parathyroid auto transplant and tracheostomy was performed while the patient was on V-A ECMO support. The surgery was completed without complications, and she was decannulated from ECMO support on the same day as the thyroidectomy. In total, she received 155 hours (6.5 days) of ECMO support.

Biopsy results revealed nodular hyperplasia and lymphocytic thyroiditis. An echocardiogram showed normal LV systolic function. Her heart rate normalized, and the rhythm changed from an AF to sinus rhythm. She remained sedated on propranolol. Her post-operative course was complicated by bleeding from her tracheal site, aspiration pneumonia, and *Escherichia coli* bacteremia which were all successfully treated. She was discharged 21 days after the thyroidectomy.

Discussion

In 2017, more than 3,000 patients were treated with LVADs.[1] In 2019 alone, 3,597 heart transplants were performed, and 4,086 new candidates were listed for heart transplantation.[6] Ventricular arrhythmias occur in 20–50% of patients supported with LVADs.[2] Chronic amiodarone therapy, while quite efficacious, is associated with thyroid dysfunction, which can occur in 5–10% of patients.[3]

Hyperthyroidism leads to an increased serum concentration of triiodothyronine (T3), which up-regulates several cardiac-specific genes that enhance contractility, improve cardiac relaxation, lower the systemic vascular resistance, increase blood volume, and elevate the baseline heart rate.[7]

Sustained tachycardia secondary to hyperthyroidism can impair LV contractility, increase atrial filling pressures, and lead to high-output HF. An untreated high-

output state may eventually lead to ventricular dilatation and persistent tachycardia resulting in CS.[8]

Cardiomyopathy is a rare complication of thyrotoxicosis and although about 6% of patients develop HF, less than 1% of the patients progress to dilated cardiomyopathy with systolic LV dysfunction and CS.[4] Thyrotoxicosis-induced CS has a mortality as high as 30%.[5] ECMO support may be required for hemodynamic support.

There is also a high incidence of AF in thyrotoxicosis. In a population-based study of 40,628 patients diagnosed with hyperthyroidism, 8.3% were diagnosed as having AF or flutter within ±30 days from the date of the diagnosis.[9]

Endothelial dysfunction, alterations in coagulation, and fibrinolytic pathways favoring a hypercoagulable state are known to occur in hyperthyroid states.[10] Elevated plasma-free thyroxine (T4) levels have also been associated with an increased risk of venous thrombosis independent of TSH levels.[11] Despite anecdotal reports that suggest that there is an increased risk of pump thrombosis in LVAD patients who develop hyperthyroidism[12] and elevated LDH, we did not encounter any issues with V-A ECMO cannula or LVAD thrombosis in our patients. Our suspicion of LVAD thrombosis was low because of the very low incidence encountered in the Heartmate III LVAD.[13]

Early recognition of thyrotoxicosis as the culprit of the CS syndrome with typical symptoms of diarrhea, fevers, and recalcitrant AF was key to initiating aggressive medical treatment. Temporary MCS in the form of V-A ECMO was initiated in a timely manner when the patient continued to decline despite maximal medical support.

Hyperthyroidism in both cases was difficult to treat despite an aggressive use of conventional medical therapy. First-line treatment with methimazole and steroids was unsuccessful, and propylthiouracil, plasmapheresis, and cholestyramine had to be added. It is important to note some cautions in medical treatment of patients with thyrotoxic CS and recurrent AF. Use of beta-blockers can worsen the CS, and amiodarone has a myocardial depressant effect and known hepatotoxicity that could worsen ischemic hepatic failure.

Both patients' hyperthyroidism continued despite medical management and underwent successful thyroidectomies. The surgeries resulted in the restoration of sinus rhythm. Case 1 required no escalation of MCS, and Case 2 was able to be weaned off of ECMO support.

Of interest, the supratherapeutic INR of 8.4 in Case 1 could be explained by the fact that thyrotoxicosis increases plasma clearance of the vitamin K-dependent clotting factors. Thus, the dose of warfarin required to prolong the prothrombin time is smaller than usual.[14]

What is unusual in case 2 is the rapid and complete normalization (< 24h) of myocardial function, which allowed for V-A ECMO weaning on the same day as the thyroidectomy after less than 6 days of support. One explanation is that, although rare, acute cardiomyopathy in hyperthyroidism occurs due to direct, toxic effects of thyroxine on the myocardium similar to catecholamine-induced cardiomyopathy. This has been previously described in pheochromocytoma and

major emotional stress.[15,16] It has also been referred to as myocardial stunning in hyperthyroidism.[17] The exact mechanism that facilitates the interaction between sympathoadrenal activity and thyroid hormones in the heart has yet to be fully elucidated.

The potential for complete normalization of myocardial function is a key factor that should prompt initiation of V-A ECMO treatment as a bridge to recovery in similar cases of thyrotoxicosis-induced CS.

Finally, successful thyroidectomy was curative, well-tolerated, and safe despite use of MCS in both cases.

A limitation to our case series is the lack of invasive hemodynamic data, but this limitation is minimal since the etiology of shock was known. The CS rapidly worsened (within 24-48 hours) and was appropriately treated. This report also lacks long-term follow up data.

Surveillance monitoring for patients with durable MCS on amiodarone should include checking free T4 and TSH levels at frequent intervals and monitoring for atrial arrhythmias. Discontinuation of amiodarone, maximizing beta blockade (if tolerated), or substitution with alternative antiarrhythmic agents should be considered when there is laboratory evidence of rising free T4 levels even if the TSH remains normal.

Conclusion

Thyrotoxicosis in patients with advanced HF can present as new onset decompensated HF leading to CS and/or de novo CS with recalcitrant atrial arrhythmias. Early recognition and appropriate treatment of a thyroid storm is critical to improve outcomes. As demonstrated, ECMO support should be considered in thyrotoxicosis-induced CS until thyroid hormone normalization is achieved. Finally, thyroidectomy is a safe and viable option to control thyrotoxicosis, and a growing body of evidence suggests that it is safe in patients with MCS.

References

1. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant. 2017;36(10):1080-6. doi:10.1016/j.healun.2017.07.005

2. Garan AR, Levin AP, Topkara V, et al. Early post-operative ventricular arrhythmias in patients with continuous-flow left ventricular assist devices. J Heart Lung Transplant. 2015;34(12):1611-6. doi:10.1016/j.healun.2015.05.018

3. Cohen-Lehman J, Dahl P, Danzi S, Klein I. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol. 2010;6(1):34-41. doi:10.1038/nrendo.2009.225

4. Dahl P, Danzi S, Klein I. Thyrotoxic cardiac disease. Curr Heart Fail Rep. 2008;5(3):170-6. doi:10.1007/s11897-008-0026-9

5. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am. 2006;35(4):663-86, vii. doi:10.1016/j.ecl.2006.09.008

6. Colvin M, Smith JM, Ahn Y, et al. OPTN/SRTR 2019 Annual Data Report: Heart. Am J Transplant. 2021;21 (Suppl 2):356-440. doi:10.1111/ajt.164925

7. Klein I, Danzi S. Thyroid Disease and the Heart. Curr Probl Cardiol. 2016;41(2):65-92. doi:10.1016/j.cpcardiol.2015.04.002

8. Biondi B. Mechanisms in endocrinology: Heart failure and thyroid dysfunction. Eur J Endocrinol. 2012;167(5):609-18. doi:10.1530/EJE-12-0627

9. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Arch Intern Med. 2004;164(15):1675-8. doi:10.1001/archinte.164.15.1675

10. Burggraaf J, Lalezari S, Emeis JJ, et al. Endothelial function in patients with hyperthyroidism before and after treatment with propranolol and thiamazol. Thyroid. 2001;11(2):153-60. doi:10.1089/105072501300042820

11. van Zaane B, Squizzato A, Huijgen R, et al. Increasing levels of free thyroxine as a risk factor for a first venous thrombosis: a case-control study. Blood. 2010;115(22):4344-9. doi:10.1182/blood-2009-11-253724

12. Rajapreyar I, Acharya D, Tallaj J, et al. Left Ventricular Assist Device Thrombosis-Amiodarone-Induced Hyperthyroidism: Causal Link? ASAIO. 2019;65(2):e18-e20. doi:10.1097/MAT.0000000000000773

13. Mehra MR, Uriel N, Naka Y, et al. A Fully Magnetically Levitated Left Ventricular Assist Device - Final Report. N Engl J Med. 2019;380(17):1618-27. doi:10.1056/NEJMoa1900486

14. Shenfield GM. Influence of thyroid dysfunction on drug pharmacokinetics. Clin Pharmacokinet. 1981;6(4):275–97.

15. Wood R, Commerford PJ, Rose AG, Tooke A. Reversible catecholamine-induced cardiomyopathy. Am Heart J. 1991;121(2 Pt1):610-3. doi: 10.1016/0002-8703(91)90740-9

16. Pavin D, Breton HL, Daubert C. Human stress cardiomyopathy mimicking acute myocardial syndrome. Heart. 1997;78(5):509-11. doi: 10.1136/hrt.78.5.509

17. Pereira N, Parisi A, Dec GW, Choo J, Hajjar R, Gordon PC. Myocardial stunning in hyperthyroidism. Clin Cardiol. 2000;23(4):298-300. doi: 10.1002/clc.4960230417