Permanent left atrial thrombi after multiple atrial fibrillation ablations: Acquired Virchow's triad?

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Introduction

Atrial fibrillation (AF) ablation can be complicated by acute thrombosis within the pulmonary veins (PVs) or on ablation catheters. To the best of our knowledge, multiple *persistent* left atrial (LA) thrombi after pulmonary vein isolation (PVI) have not been reported.

Case report

A 72-year-old male patient presented with persistent palpitations owing to symptomatic AF. He was referred to the electrophysiology clinic by his cardiologist for palpitations that interfered with his daily routine and required multiple hospital admissions. Physical examination was unremarkable, with normal vital signs and regular heart sounds. His electrocardiogram (ECG) during the visit showed sinus bradycardia and possible anterior infarct.

Past medical history

The patient was first diagnosed with paroxysmal AF 3 years prior to this clinic visit. He received multiple rhythm control strategies in the past, including electrical cardioversion, medical therapy with sotalol, and 3 catheter ablations. During his last ablation, an anterior line isolating the left vein from left atrial appendage to left upper pulmonary vein was created. The ridge line was created on the left side. Right-sided veins were reconnected. Preprocedural transesophageal echocardiography (TEE) reports before prior ablations at the outside institution showed absence of any LA thrombi. Owing to a new occurrence of atrial tachycardia, which required electrical cardioversion, the patient was referred for electrophysiologic mapping and possible ablation. The patient had a history of hyperlipidemia and essential hypertension. He had undergone hernia repair, eye surgery, and back surgery in the past without any complications. Finally, he did not have any family history of cardiac disease or any hypercoagulable disorder. His daily medications were aspirin 81 mg daily, sotalol 80 mg twice daily (BID), metoprolol succinate 25 mg daily, rivaroxaban 20 mg daily, olmesartan 5 mg daily, rosuvastatin 5 mg daily, triamterene-hydrochlorothiazide 37.5-25 mg daily, and silodosin 80 mg BID.

We first recommended empirically increasing the sotalol to 120 mg BID. On follow-up, the patient was initially doing well, without palpitations or documented tachycardia on his wearable heart rate monitor. He reported good compliance to his medications, including the rivaroxaban. However, 7 months later, he developed episodes of atrial tachycardia requiring emergency room visit and cardioversion. Because of his atrial tachycardia, we planned on performing electrophysiology study, including detailed mapping of the PVs, and possibly creating lines of ablation along the LA roof, mitral isthmus, and regions of scar.

Investigations

On the day of the planned ablation, preoperative TEE showed multiple sub-centimeter mobile masses consistent with thrombi in the LA, particularly at the junction of PVs (TEE-1: Figure 1A). The largest of such masses was a mobile 1.5 cm filamentous lesion attached to the ridge between the LA appendage and left upper PV (warfarin ridge), oscillating between the LA and PV (Figure 1B) (Supplemental Videos 1 and 2). In addition to that, multiple mobile thrombi adjacent to the right upper pulmonary vein were noted (Supplemental Videos 3 and 4). The planned ablation was aborted. There was no evidence of atrial standstill on ECG or on imaging.

Since the patient developed these thrombi despite good compliance to rivaroxaban for more than a year, the anticoagulation regimen was switched to warfarin bridged with enoxaparin. On warfarin, the patient's international normalized ratio remained consistently within therapeutic range (2.0–3.0). Repeat TEE 3 months later showed persistent findings (TEE-2, Figure 2).

Management (medical/interventions)

Owing to the persistent thrombi despite therapeutic warfarin, international normalized ratio goal was increased to 2.5–3.5.

KEYWORDS Atrial fibrillation; Catheter ablation; Anticoagulation; Complications; Thrombogenicity
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KEY TEACHING POINTS

- Three factors predispose to clot formation: venous stasis, endothelial damage, and a hypercoagulable state.
- Patients with atrial fibrillation have atrial myopathy, which promotes an independent clinical substrate associated with thrombogenicity. Atrial myopathy may be related to fibrosis from aging, atrial stretch, or inflammation.
- There is increased possibility of thrombogenicity of the left atrium particularly at the junction of pulmonary veins and left atrial wall after multiple catheter ablations.

Subsequent TEE showed unchanged thrombi (TEE-3, Figure 3). Warfarin was switched to subcutaneous enoxaparin. After 3 months of therapeutic doses of enoxaparin, as evidenced by heparin anti-Xa levels, the patient's thrombi persisted (TEE-4, Supplemental Figure 1). The patient was switched back to rivaroxaban and the thrombi remain unresolved.

Follow-up

On subsequent clinic follow-up, the patient reported no longer having palpitations for the past several months. His ECG still showed atrial flutter with controlled ventricular response. Owing to persistent LA thrombi and failure of ablations in the past with relatively controlled symptoms, we elected to defer further invasive interventions. Given the ease of use of direct oral anticoagulant, the patient remains on rivaroxaban. Laboratory investigations, including factor V Leiden, anti-thrombin, lupus anticoagulant, and anti-cardiolipin antibodies, did not reveal any additional cause of hypercoagulability or any evidence of malignancy. A timeline of clinical, diagnostic, and therapeutic events is depicted in Supplemental Figure 2.

Discussion

We describe a case of multiple AF ablations with PVI creating persistent LA thrombi resistant to anticoagulation therapy with warfarin, low-molecular-weight heparin, and rivaroxaban. Prior to these LA thrombi, our patient did not have a history of venous or arterial thromboses. Excluding AF, he was not known to have any specific systemic conditions, such as malignancy or behavioral risk factors, that promoted thrombosis. Family history and hypercoagulable investigations were negative. We received the documentation of prior TEE without any evidence of LA thrombi preceding our patient's prior AF ablations. Given the cumulative findings of multiple ablations and the location of the thrombi near the junction of the PV and LA, these findings may indicate a thrombogenic milieu caused by recurrent ablative injury.

The pathogenesis of these LA thrombi is not clear. Over a century ago, Rudolf Virchow reported 3 factors that predispose to clot formation.[1] These factors are venous stasis, endothelial damage, and a hypercoagulable state. Thrombosis in AF ablation may represent a more complex entity. Patients with AF have atrial myopathy, which promotes an independent clinical substrate associated with thrombogenicity. Atrial myopathy may be related to fibrosis from aging, atrial stretch, or inflammation.[2] Instrumentation in catheter ablation also poses a risk for thrombosis. In a study of 232 patients undergoing catheter ablation, Ren and colleagues[3] showed LA thrombus formation in about 10% of patients on intracardiac echocardiography despite aggressive intraprocedural anticoagulation. The majority of the thrombi were found to be attached to the relatively stable sheaths

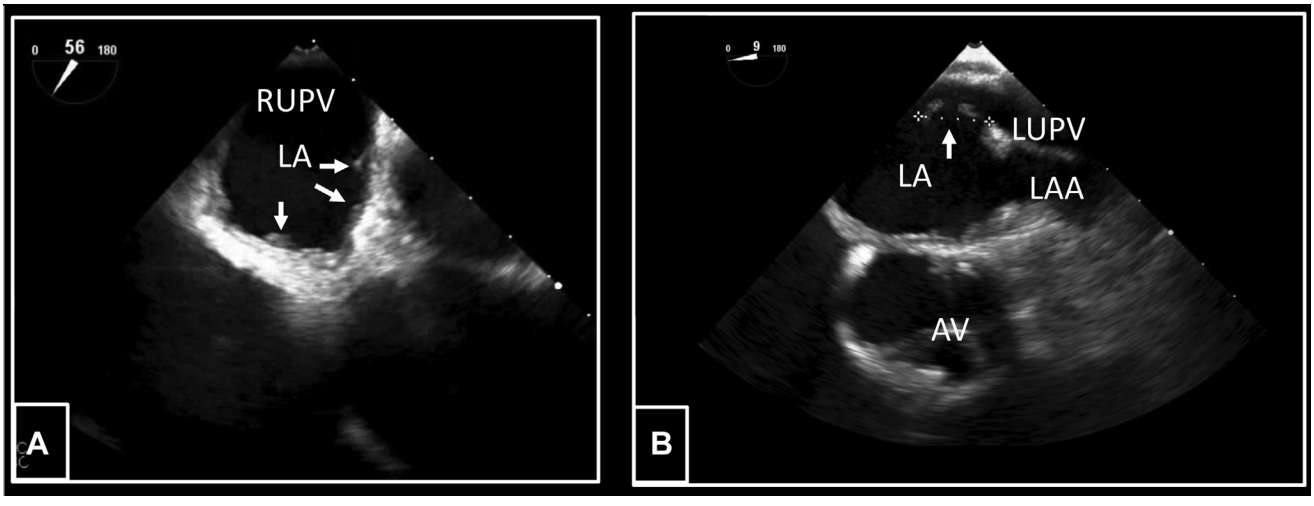

Figure 1 TEE-1. **A:** Preprocedure transesophageal echocardiography (TEE) revealed multiple, mobile elements encircling the right upper pulmonary veins (RUPV) (*white arrows*). **B:** TEE-1 demonstrating 1.5 cm filamentous thrombus anchored at the ostium of the left upper pulmonary vein (LUPV) extending into left atrium (LA). AV = aortic valve; LAA = left atrial appendage.

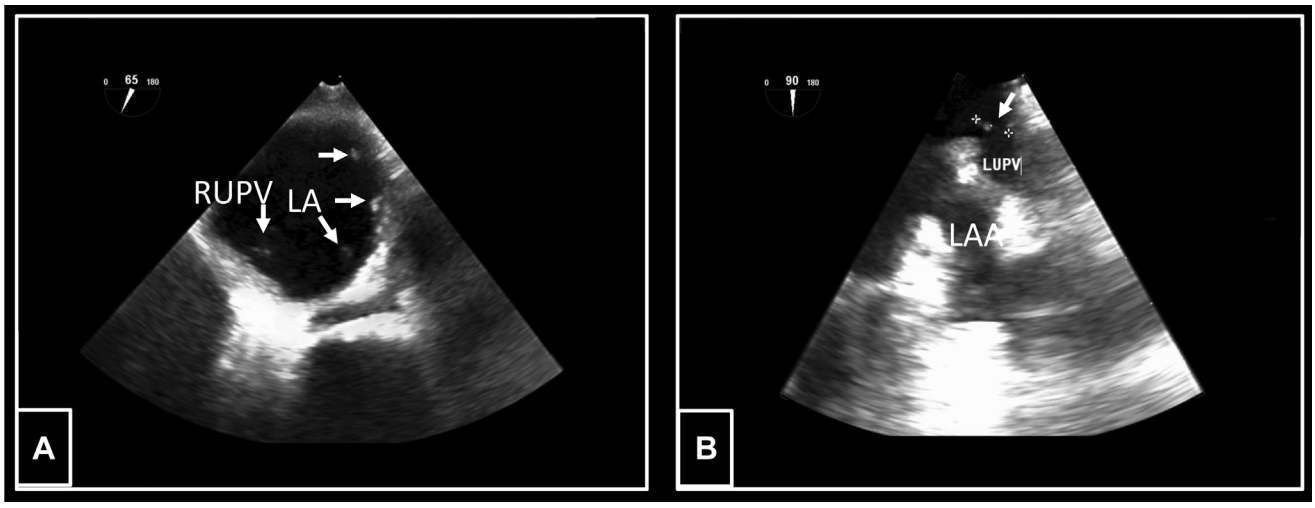

Figure 2 TEE-2. **A:** Despite switching oral anticoagulation from rivaroxaban to therapeutic warfarin with goal international normalized ratio 2.0–3.0, transesophageal echocardiography (TEE)-2 demonstrated persistence of multiple left atrial thrombi (*white arrows*). **B:** TEE-2 showing fixed left atrial thrombus at the ostium of the left upper pulmonary vein (LUPV) (*white arrow*). LA = left atrium; LAA = left atrial appendage; RUPV = right upper pulmonary vein.

and mapping catheters rather than the ablation catheter that was being manipulated.[3] It is feasible that instrumentation stasis rather than the delivery of radiofrequency (RF) energy can play a role in thrombogenesis. However, in our patient's case, the multiple thrombi were found a month after his last ablation and were located along the ostia of the previously isolated PVs. This suggests that local endothelial damage is a causative factor. Furthermore, platelet activation, coagulation cascade activation, and fibrinolytic inhibition from RF ablation may also have promoted thermogenesis (Supplemental Figure 3). Endothelial damage from repeated RF ablation injury and subsequent inflammation in the setting of AF could have resulted in a nefarious thrombotic climate.

The appropriate management strategy of thrombi formed after ablation is unknown. Ninety percent of thrombi in catheter ablation are usually eliminated from the LA by withdrawal of the sheath or catheter into the right atrium.[3] This was not applicable to our case, given that our patient's thrombi adhered to the LA walls. Kuroda and colleagues[4] reported a presentation of a giant LA thrombus that was also resistant to anticoagulation and required surgical excision. In our case, owing to multiple small thrombi, surgical resection was not feasible and involved considerable risk. The exact risk of embolization of multiple, small re-endothelialized thrombi is unknown. Systemic anticoagulation has not led to progression of thrombi size or overt clinical embolic complications. Combination therapy with anticoagulant and antiplatelets, such as dual or triple therapy, in this setting has not been tested, and the risks of bleeding may outweigh benefits. Use of a cerebral protection device to aid in performing a catheter ablation therapy has been

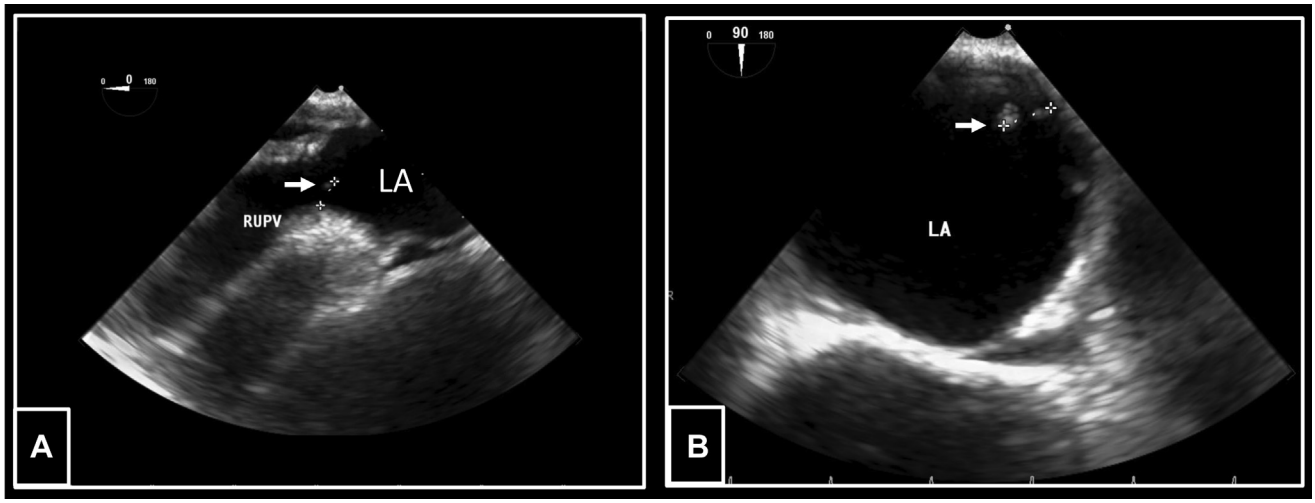

Figure 3 TEE-3. Transesophageal echocardiography after over a year of warfarin therapy with an elevated international normalized ratio goal of 2.5–3.5 demonstrating resistant thrombi. **A:** Image highlights a 0.47-cm thrombus adjacent to the right upper pulmonary vein (RUPV). **B:** Image displays a 0.56-cm thrombus at the roof of the left atrium (LA).

previously reported.[5] However, performing another ablation may have caused harmful progression in our patient, especially if the thrombi were induced as a result of endothelial damage. Our patient's symptoms continue to represent a clinical challenge.

Conclusion

We report a rare case of multiple LA thrombi formed at the LA-PV junctions after multiple AF ablations using PVI. The thrombi persisted despite uninterrupted anticoagulation with different oral and injectable agents. This case highlights a possible permanent complication of AF ablation owing to recurrent RF injury in a thrombogenic milieu in the setting of atrial myopathy. Further research is needed for understanding of the mechanism, the prevalence, and the optimal management of this challenging problem.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at 10.1016/j.hrcr.2022.07.015.

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