Left atrial appendage thrombus formation less than 24 hours after empirical cryoballoon-based left atrial appendage isolation: A serious warning

Roland Richard Tilz, MD, FESC, FEHRA, FHRS, Spyridon Liosis, MD, Julia Vogler, MD, Jan C. Reil, MD, Charlotte Eitel, MD, Christian-H. Heeger, MD

From the Department of Cardiology, Angiology and Intensive Care Medicine, University Heart Center Lübeck, Medical Clinic II, Lübeck, Germany.

Introduction

Pulmonary vein isolation (PVI) is an effective treatment strategy for patients with paroxysmal atrial fibrillation (AF).[1,2] However, in patients with persistent AF (PersAF) and long-standing PersAF, PVI is associated with limited success rates, often requiring multiple procedures for those not responding to PVI.[3] More extensive ablation strategies, including ablation of complex fractionated atrial electrograms, linear lesions, and rotors, have been performed with the aim of improving clinical outcome. However, recent findings remain controversial.[4–7] Therefore, current research is focusing on ablation strategies that potentially enhance procedural success, particularly in nonresponders to PVI. In this context, additional targets outside the PVs have been suggested.[8,9] Di Biase and colleagues[8,10] demonstrated that ectopic beats from the left atrial appendage (LAA) are able to initiate and perpetuate AF, and empirical electrical isolation of the LAA (LAAI) using radiofrequency (RF) current in addition to PVI has been shown to increase clinical success. Although potentially effective, this strategy may cause electromechanical dissociation of the LAA and therefore was assumed to be associated with an increased risk for LAA thrombus formation and subsequent thromboembolic events despite oral anticoagulation.[11] However, available data are limited, vary across a wide range, and lack long-term assessments.[10–12] Although data on the thrombogenicity of RF-based LAA isolation are conflicting, no increased risk for LAA thrombus or thromboembolism has been reported after second-generation cryoballoon (CB2, Arctic Front Advance, Medtronic, Minneapolis, MN)–based LAAI.[13] Here we report a case of LAA thrombus formation occurring less than 24 hours after CB2-based LAAI despite oral anticoagulation.

KEY TEACHING POINTS

- Empirical electrical isolation of the left atrial appendage (LAAI) using radiofrequency (RF) current in addition to pulmonary vein isolation has been shown to increase clinical success. Although potentially effective, this strategy may be associated with an increased risk for left atrial appendage (LAA) thrombus formation and subsequent thromboembolic events.
- LAA thrombus formation is possible after empirical LAAI using a second-generation cryoballoon (CB2).
- Although we report the case of a single patient, our finding highlights the importance of screening patients for LAA thrombi after RF- or CB2-based LAAI.
- LAA closure seems to be a reasonable strategy to prevent LAA thrombus formation after LAAI.

Case report

A 74-year-old male patient (CHA_2DS_2-VASc score 2, HAS-BLED score 2) suffered from recurrent PersAF after CB2-based PVI in July 2015 despite antiarrhythmic drug therapy with flecainide (2 × 100 mg) and oral anticoagulation with apixaban (2 × 5 mg). The patient was scheduled for a second ablation procedure. He was unwilling to take oral anticoagulation. Because of PersAF after initial PVI, an empirical

KEYWORDS Atrial fibrillation; Catheter ablation; Cryoballoon; Left atrial appendage isolation; Stroke; Thrombus formation
(Heart Rhythm Case Reports 2019;5:124–127)

Dr Heeger received travel grants and research grants by Medtronic, Claret Medical, SentreHeart, Biosense Webster, Pfizer, and Cardiofocus. Dr Tilz received travel grants from St. Jude Medical, Topera, Biosense Webster, Daiichi-Sankyo, and SentreHeart; Speaker's Bureau honoraria from Biosense Webster, Biotronik, Pfizer, Topera, Bristol-Myers Squibb, Bayer, and Sano Aventis; and research grants by Cardiofocus. All other authors have no relevant disclosures. **Address reprint requests and correspondence:** Dr Roland Richard Tilz, Medizinische Klinik II, Kardiologie, Angiologie, Intensivmedizin, Universitäres Herzzentrum Lübeck, Universitätsklinikum Schleswig-Holstein (UKSH), Ratzeburger Allee 160, D-23538 Lübeck, Germany. E-mail address: tilz6@hotmail.com.

https://doi.org/10.1016/j.hrcr.2018.11.010

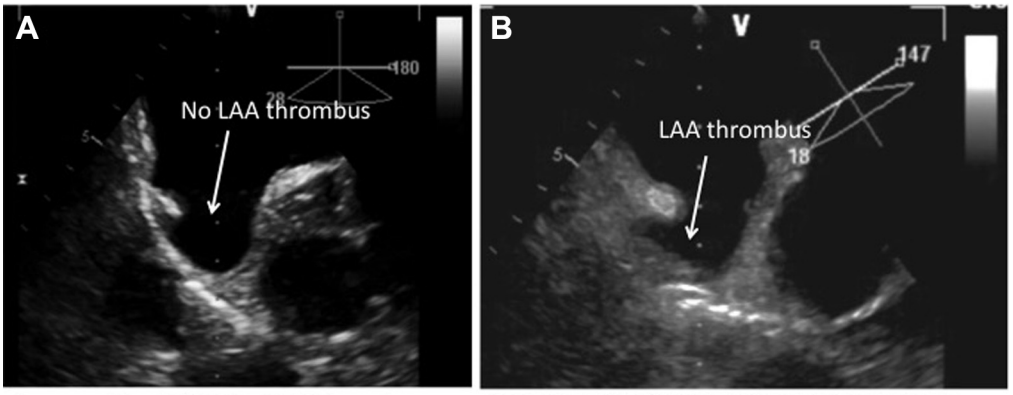

Figure 1 Transesophageal echocardiographic (TEE) images of the left atrial appendage (LAA). **A:** Preprocedural analysis with no evidence of thrombus formation within the LAA. **B:** Postprocedural analysis <24 hours after LAA isolation (LAAI) with evidence of an LAA thrombus. OAC = oral anticoagulation.

isolation of the LAA before LAA closure was suggested, and the patient consented to this treatment strategy.

Preprocedural transesophageal echocardiography (TEE) revealed normal flow within the LAA (90 cm/s) and no LAA smoke or thrombus formation (Figure 1A). The ablation procedure was scheduled for the next day. Only the morning dose of apixaban was withheld. When the procedure started, the patient was in stable sinus rhythm. During the procedure, an activated clotting time >300 seconds was maintained using heparin. All PVs showed durable PVI. Ostial potentials were ablated around the left common pulmonary vein. Using the 28-mm CB2 in combination with a 20-mm Achieve catheter, the LAA was isolated during the first CB2 application after 240 seconds. Cryoapplication time was 300 seconds, and minimum temperature was –50°C (Figure 2). Afterward, a bonus freeze application of 300 seconds was applied with a minimal temperature of –49°C. LAAI was confirmed by entrance and exit block. Left phrenic nerve stimulation was performed during the CB2 applications to prevent phrenic nerve injury. Apixaban 2.5 mg was started 6 hours after the procedure and increased to 5 mg twice per day on the next day.

Contrast-enhanced computed tomography of the heart scheduled on day 1 after the procedure to plan epicardial LAA closure revealed a thrombus at the distal LAA. TEE confirmed the LAA thrombus and revealed LAA flow of 60 cm/s (Figure 1B). To dissolve the LAA thrombus, oral anticoagulation with phenprocoumon (international normalized ratio 2–3) was initiated. The patient was in stable sinus rhythm with flecainide 100 mg twice per day until discharge. Follow-up TEE 6 weeks later revealed evidence of a persistent LAA thrombus. Repeat TEE 12 weeks postablation revealed no evidence of LAA thrombus. To prevent further LAA thrombus formation, an LAA closure procedure was planned. The epicardial LAA ligation device features a snare with a maximum snare expansion diameter of 45 mm. Because the ostium of the LAA was measured as 47 mm by computed tomography, an endocardial approach was scheduled. An invasive electrophysiological study using a spiral mapping catheter demonstrated persistent LAAI. LAA closure using a 28-mm Amplatzer Amulet device (Abbott, Chicago, IL) was performed (Figure 3). Antiplatelet therapy with clopidogrel and aspirin was administered for 6 weeks after device implantation. No recurrence of AF or thromboembolism occurred during short-term follow-up of 3 months.

Discussion

Here we report a case of rapid LAA thrombus formation that occurred <24 hours after CB2-based LAAI. Loss of LAA mechanical function after LAAI was previously suggested to potentially increase thromboembolic risk.[9,11] Although possibly effective, the optimal ablation strategy for LAAI remains unclear, and assessments of postprocedural LAA thrombus formation are inconsistent.[10–12] In the BELIEF (Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Longstanding Persistent Atrial Fibrillation Undergoing Catheter Ablation) trial[10] and in a study by Bordignon and colleagues,[12] no increased rates of LAA thrombus formation and thromboembolism were observed for LAAI patients. However, Heeger and colleagues[14] found an increased rate of postprocedural LAA thrombus and thromboembolism after LAAI. Although different ablation strategies might explain this discrepancy, the mechanism of electrical LAAI with consecutive loss of mechanical contraction resulting in thrombus formation presumably occurs regardless of the strategy.[11]

Using the CB2, a more distal, circular LAA isolation is performed compared to RF-based wide-area LAA isolation.[11,14] Therefore, the isolated area might be smaller, which might reduce the risk of thrombus formation. Yorgun and colleagues[13] recently evaluated CB2-based LAAI in addition to PVI. In their study, a favorable outcome compared to the PVI-only strategy without any postprocedural LAA thrombus formation and no increase in thromboembolism was observed in the LAAI group.[13] In contrast to the previous study, we identified LAA thrombus formation in the first patient with CB2-based LAAI at our clinic.

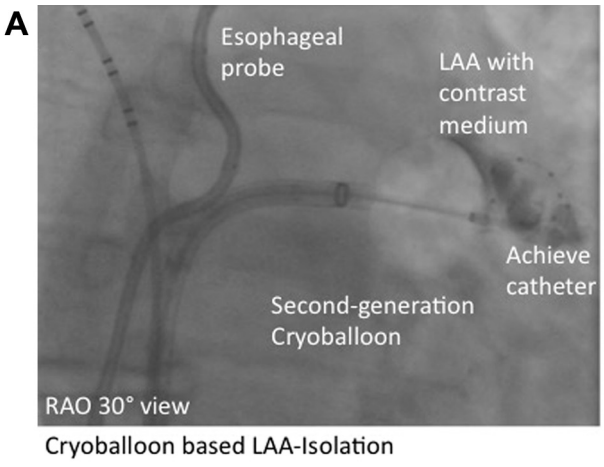

Figure 2 Second-generation cryoballoon-based isolation of the left atrial appendage (LAA). **A:** Fluoroscopic image in right anterior oblique (RAO) 30° view showing contrast medium–verified complete occlusion of the LAA by the second-generation cryoballoon. The Achieve spiral catheter is placed inside the LAA. **B:** Surface and intracardiac electrocardiograms at baseline showing reconduction into the LAA. **C:** Surface and intracardiac electrocardiograms after LAA isolation with pacing from the Achieve catheter inside the LAA and evidence of conduction dissociation between the LAA and the ventricular signal. A = atrium; V = ventricle.

Although this might be a remarkable coincidence, the tremendous clinical relevance of potential iatrogenic cerebral thromboembolism after LAAI underlines the need to evaluate this controversial finding in large multicenter trials. As a result of our observation, the protocol for postprocedural oral anticoagulation after CB2-based LAAI was changed at our institution so that full-dose novel oral anticoagulants are started after 6 hours (not half-dose as reported in this case report).

Closure of the LAA after LAAI may be a viable option to reduce the risk for thromboembolic complications without the need for lifelong oral anticoagulation and its potential consequences.[15] For this purpose, LAA closure was performed in our patient to prevent recurrent LAA thrombus formation and potential thromboembolism.

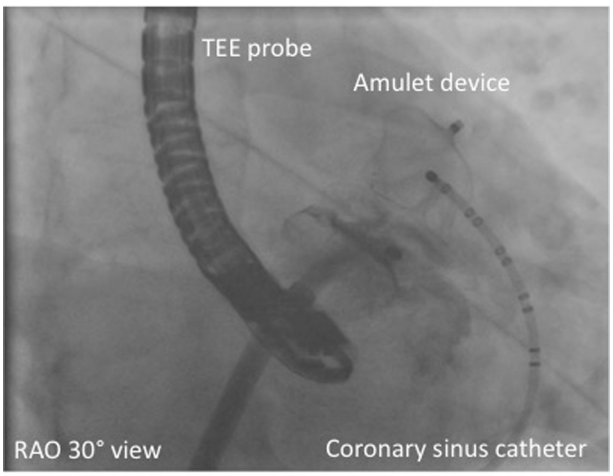

Figure 3 Left atrial appendage closure. Fluoroscopic image in the right anterior oblique (RAO) 30° view showing the final image after left atrial appendage closure using an Amulet device. TEE = transesophageal echocardiography.

Conclusion

Here we present a case of CB2-based empirical LAAI and subsequent LAA thrombus formation despite sufficient oral anticoagulation. Although we report the case of a single patient, our finding highlights the importance of screening patients for LAA thrombi after RF- or CB2-based LAAI. Clinical trials and registries are necessary to draw final conclusions.

References

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275–e444.
2. Tilz RR, Heeger CH, Wick A, et al. Ten-year clinical outcome after circumferential pulmonary vein isolation utilizing the Hamburg approach in patients with symptomatic drug-refractory paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol 2018;11:e005250.
3. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg sequential ablation strategy. J Am Coll Cardiol 2012;60:1921–1929.
4. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812–1822.
5. Fink T, Schluter M, Heeger CH, et al. Stand-alone pulmonary vein isolation versus pulmonary vein isolation with additional substrate modification as index ablation procedures in patients with persistent and long-standing persistent atrial fibrillation: the randomized Alster-Lost-AF trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation). Circ Arrhythm Electrophysiol 2017;10:e005114.
6. Vogler J, Willems S, Sultan A, Schreiber D, Luker J, Servatius H, Schaffer B, Moser J, Hoffmann BA, Steven D. Pulmonary vein isolation versus defragmentation: the CHASE-AF clinical trial. J Am Coll Cardiol 2015;66:2743–2752.
7. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628–636.

8. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation 2010;122:109–118.
9. Di Biase L, Natale A. Left atrial appendage after electrical isolation: to occlude or not to occlude, that is the question. Circ Arrhythm Electrophysiol 2016;9:e004372.
10. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage isolation in patients with longstanding persistent AF undergoing catheter ablation: BELIEF trial. J Am Coll Cardiol 2016;68:1929–1940.
11. Rillig A, Tilz RR, Lin T, et al. Unexpectedly high incidence of stroke and left atrial appendage thrombus formation after electrical isolation of the left atrial appendage for the treatment of atrial tachyarrhythmias. Circ Arrhythm Electrophysiol 2016;9:e003461.
12. Bordignon S, Perrotta L, Dugo D, Bologna F, Nagase T, Fuernkranz A, Chun KRJ, Schmidt B. Electrical isolation of the left atrial appendage by Maze-like catheter substrate modification: a reproducible strategy for pulmonary vein isolation nonresponders? J Cardiovasc Electrophysiol 2017;28:1006–1014.
13. Yorgun H, Canpolat U, Kocyigit D, Coteli C, Evranos B, Aytemir K. Left atrial appendage isolation in addition to pulmonary vein isolation in persistent atrial fibrillation: one-year clinical outcome after cryoballoon-based ablation. Europace 2017;19:758–768.
14. Heeger CH, Rillig A, Geisler D, et al. Left atrial appendage isolation in patients not responding to pulmonary vein isolation. Circulation 2019;139:712–715.
15. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW; EWOLUTION Investigators. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J 2016;37:2465–2474.