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CASE REPORT

A 79-year-old woman with atrial fibrillation and new onset of heart failure

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Abstract

As an alternative to oral anticoagulation, percutaneous left atrial appendage (LAA) closure is an increasingly performed procedure to prevent arterial embolism in patients with non-valvular atrial fibrillation. Besides procedure-related complications, residual leaks, device-related thrombus formation, and dislocation of the LAA occluder have been observed during follow-up. Heart failure as a consequence of interventional LAA closure has not been reported so far. This case report describes a 79-year-old lady with permanent non-valvular atrial fibrillation presenting with New York Heart Association Class IV heart failure. Symptoms had started immediately after attempted LAA closure 11 months before. Transoesophageal echocardiography demonstrated two devices in the LAA, a large peri-device leak, a mobile LAA thrombus, a right atrial appendage thrombus, and shunting via a patent foramen ovale. Under a maximally tolerated dose of heart failure medication and edoxaban, the patient remains without bleeding or embolism in New York Heart Association Class II. Because of its unique anatomical and endocrine properties, the LAA plays an important role in situations of pressure and volume overload. Interventional LAA closure interacts unfavourably with left atrial compliance and reservoir function. Atrial and brain natriuretic peptide secretion is known to be significantly reduced after LAA closure. Both mechanisms may result in the development of heart failure. Attempted LAA closure—instead of being the solution—may create new serious problems. Development of heart failure should be assessed, and a systematic search for late leaks after LAA closure should be performed in trials investigating safety and efficacy of this intervention.

Keywords Atrial fibrillation; Congestive heart failure; Left atrial appendage closure; Left atrial appendage thrombus; Peri-device leak; Transoesophageal echocardiography

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Introduction

As an alternative to oral anticoagulation (OAC), percutaneous left atrial appendage (LAA) closure is an increasingly performed procedure to prevent arterial embolism in patients with non-valvular atrial fibrillation (nAF). According to the 2016 European Society of Cardiology guidelines for the management of atrial fibrillation, interventional LAA closure may be considered for stroke prevention in patients with nAF and contraindications for long-term anticoagulant treatment, for example, those with a previous life-threatening bleed without a reversible cause (Class IIb, Level B recommendation).[1] Percutaneous LAA closure, however, is not without risks. Besides procedure-related complications, residual leaks, device-related thrombus formation, and dislocation of the LAA occluder have been described during follow-up.[2,3]

Because over 90% of atrial thrombi are assumed to form in the LAA,[4] this structure has been referred to as 'our most lethal human attachment'.[5] The LAA, however, plays an important endocrine and haemodynamic role in clinical situations of pressure and volume overload and is the main site of release of atrial natriuretic peptide (ANP), which regulates blood pressure and volume by diuretic, natriuretic, and vasodilatory effects.[6] With regard to this neglected aspect of LAA function, a case is presented with New York Heart Association (NYHA) Class IV heart failure developing after interventional LAA closure.

Case report

A 79-year-old woman was admitted in February 2015 because of dyspnoea and generalized oedema. The patient had ever been a small and very slim person (body mass index 16.4).

In 2012, focal myocarditis and paroxysmal nAF (CHA_2DS_2-VASc score 5 and HAS-BLED score 2) had been diagnosed. Transthoracic echocardiography showed a slightly reduced systolic left ventricular function with basolateral hypokinesia, normal diastolic left ventricular function (septal e′ velocity 10 cm/s, E/e′ ratio 5), and prolapse of both atrioventricular valves without significant regurgitation. During follow-up under anticoagulant therapy with unfractionated heparin, phenprocoumon, or rivaroxaban (15 mg/day), multiple bleeding events had occurred (thigh haematoma, spontaneous haematoma of abdominal muscles requiring surgery, and intraocular bleeding). Therefore, the patient was felt not to be a candidate for OAC, and in March 2014, interventional occlusion of the LAA had been performed elsewhere using a 24 mm WATCHMAN device (Boston Scientific, Marlborough, MA, USA). Because of a large peri-device leak detected by transoesophageal echocardiography (TOE) during follow-up, in November 2014, in the same institution, a 12 × 5 mm Amplatzer Vascular Plug III (St. Jude Medical, St. Paul, MN, USA) had additionally been implanted into the LAA. The procedure was complicated by pericardial tamponade necessitating pericardiocentesis. Since the first procedure in March 2014, the patient had noticed progressive dyspnoea, leg oedema, and a gradual increase of weight from 41 to 49 kg.

On admission to our hospital in February 2015, the patient was on a medication with acetylsalicylic acid 100 mg/day, clopidogrel 75 mg/day, torasemide 5 mg/day, metoprolol 47.5 mg/day, and ramipril 2.5 mg/day. Blood pressure was 130/90 mmHg, and heart rate was 92 b.p.m. and irregular. The patient showed jugular venous distension, hepatomegaly, leg oedema, and anasarka of the lumbar region, and there was bilateral pleural effusion. Laboratory findings included microcytic anaemia (haemoglobin 10 g/dL, mean corpuscular haemoglobin 18.2 pg, and mean corpuscular haemoglobin concentration 28.7 g/dL), elevation of lactate dehydrogenase (383 U/L), γ-glutamyltransferase (107 U/L), alkaline phospatase (173 U/L), and pro-brain natriuretic peptide (3956 pg/mL). Electrolytes, renal function, and serum electrophoresis were normal. D-dimer level was normal on two occasions, and blood coagulation testing with respect to hypocoagulation or hypercoagulation was unremarkable. The electrocardiogram showed atrial fibrillation, low voltage, and T-wave inversion in the precordial leads similar to 2012 without any change during follow-up. Coronary angiography had been performed in 2011, 2012, and 2014 during attempted LAA closure and revealed non-significant coronary artery disease without progression over time. Chronic obstructive pulmonary disease was well controlled by inhalation therapy, and pulmonary function testing remained unchanged. Holter monitoring on two occasions demonstrated good rate control with a mean heart rate of 84 b.p.m. Transthoracic echocardiography revealed a left ventricle of normal size with normal diastolic function (septal e′ velocity 10 cm/s, E/e′ ratio 5), slight basolateral hypokinesis, and an ejection fraction of 50% identical to 2012. The right atrium and right ventricle were enlarged, and there was tricuspid valve prolapse with severe tricuspid regurgitation (peak velocity 2.9 m/s) and low-grade pulmonary hypertension, which both had not been present 3 years before. There was neither pericardial effusion nor signs of pericardial constriction. TOE (Supporting information) demonstrated incomplete LAA closure despite the presence of two devices with a 4 mm leak between the LAA wall and both occluders (*Figure 1A*) and a large mobile thrombus (1.8 × 1.0 × 0.9 cm) within the LAA (*Figure 1B*). In addition, there was a right atrial appendage thrombus (1.2 × 1.2 cm, *Figure 1D*) and haemodynamically insignificant bidirectional shunting through the interatrial septum via a patent foramen ovale (*Figure 1C*). After intravenous diuretic therapy, the oedema slowly regressed and the patient lost 6 kg of weight. Anticoagulant therapy with unfractionated heparin, followed by apixaban 2.5 mg b.i.d., was initiated because of both left and right atrial appendage thrombi. After 15 days, she was discharged with a heart failure medication of metoprolol 95 mg/day, ramipril 2.5 mg/day, spironolactone 25 mg/day, and furosemide 80 mg/day.

Over the next months, the patient was hospitalized four times because of heart failure and anaemia necessitating transfusion of packed red cells and intravenous iron supplementation. Gastroscopy and colonoscopy showed no obvious bleeding source. Because of epigastric discomfort, apixaban was changed to dabigatran 75 mg b.i.d. However, the patient developed a skin rash, and anticoagulation was switched to edoxaban 30 mg/day. Under a maximally tolerated dose of heart failure medication, the patient remained without bleeding or embolic events in NYHA Class II heart failure during follow-up.

Discussion

Atrial fibrillation is the most common sustained cardiac arrhythmia affecting mainly elderly people, with embolic stroke occurring in 5% of non-anticoagulated patients every year. The risk of stroke increases substantially with age.[1] OAC for stroke prevention has the disadvantage of bleeding complications especially in older patients and in those with low body weight.[7] Most probably, the bleeding events in our patient resulted from overanticoagulation by prescribing standard anticoagulant doses for this small and underweight lady.[8] In addition, there may have been insufficient laboratory

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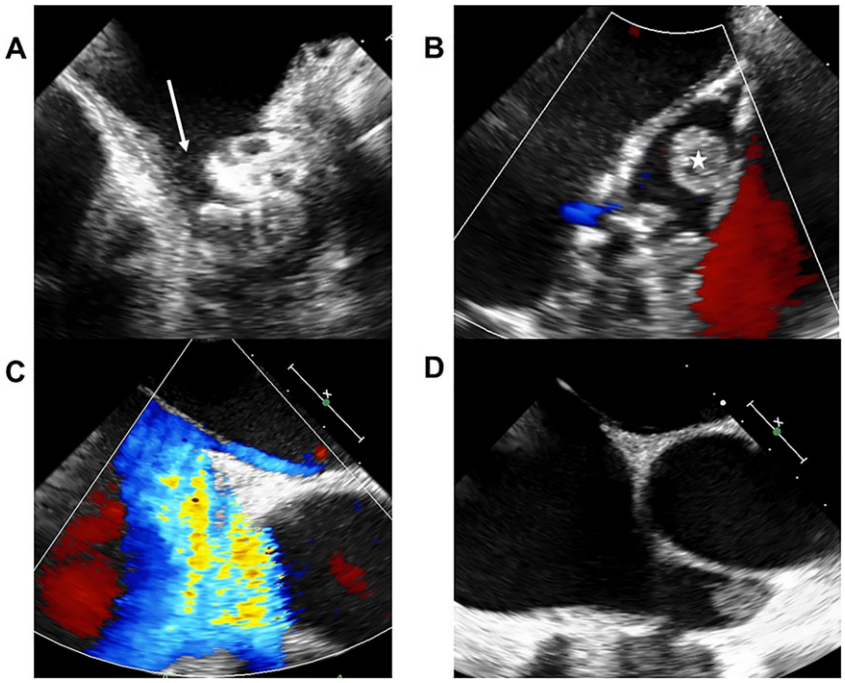
Figure 1 Transoesophageal echocardiography demonstrating incomplete left atrial appendage (LAA) closure despite the presence of two devices with a 4 mm leak (arrow) between LAA wall and both occluders (A). Within the LAA, there is a large mobile thrombus (asterisk, B). In addition, there is bidirectional shunting through the interatrial septum via a patent foramen ovale (C) and a right atrial appendage thrombus (D).



monitoring during therapy with a vitamin K antagonist. Because of multiple bleeding events during anticoagulation and a CHA_2DS_2-VASc score of 5, the patient had undergone interventional LAA closure. Eight months later, a second device had been implanted in the LAA because during a follow-up TOE, a significant peri-device leak had been detected. Beginning after the first procedure, the patient progressively developed congestive heart failure (NYHA Class IV).

From animal studies, it is known that the LAA myocardium has a higher distensibility than the left atrial myocardium. After exclusion of the LAA from the blood circulation, a decrease in left atrial compliance has been described in animals.[9–11] Because the LAA is 2.6 times as compliant as the left atrial body, this structure contributes significantly to left atrial reservoir function and is essential for the adaption to pressure and volume overload.[12] Thus, one reason for the new onset of heart failure in our patient may be the fact that interventional LAA closure interacts unfavourably with left atrial compliance and reservoir function.

In addition, the LAA is an important structure for the release of ANP and brain natriuretic peptide. In normal human hearts, ANP concentration is 40-fold higher in the LAA than in the remainder of the atrial free wall and in the ventricular endocardium.[13] Because natriuretic peptides play an important role in fluid regulation and volume homeostasis, LAA closure may impede the physiological regulation in heart failure. A significant decrease of ANP and brain natriuretic peptide serum levels after interventional LAA closure has been described, although only in small cohorts.[14,15]

Up to now, there is only one randomized trial comparing LAA closure with OAC.[2] The development of heart failure, however, was not investigated in this study. Similarly, in the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies evaluating percutaneous LAA closure, new onset of heart failure after the procedure or measurements of natriuretic peptides are not included in the study design.[16] In a recent publication, rehospitalizations for heart failure were reported in 17% of the patients after interventional LAA closure; however, the development of heart failure was attributed to pre-existing cardiac disease in this study.[17] Peri-device leaks and thrombus formation on the device may occur as a complication of LAA closure even years after the procedure, and therapeutic options for these situations are still unclear.[18,19] Progressive left atrial enlargement is a well-known phenomenon in permanent nAF and has also been documented after interventional LAA closure.[20] This may result in the development of new peri-device leakage of an initially completely closed LAA during follow-up.[21] Thrombus formation within the LAA in the presence of incomplete LAA closure with a persistent leak may lead to embolic complications and necessitates OAC despite device implantation. Further potentially disastrous consequences in our patient were a right atrial appendage thrombus and bidirectional interatrial shunting through a

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patent foramen ovale with the additional risk of paradoxical embolism.

Apart from haemodynamic and endocrine consequences, LAA closure has been shown to affect glycolysis, tricarboxylic acid, urea, and lipidome metabolism.[22,23] At present, the clinical relevance of this phenomenon during long-term follow-up is unknown.

Attempted LAA closure—instead of being the solution—may create new serious problems. Thus, risk and benefit of this procedure has to be thoughtfully considered in each patient. Development of heart failure should be assessed in every patient, and a systematic search for late leaks after LAA closure should routinely be performed in trials investigating safety and efficacy of this intervention. Long-term haemodynamic, endocrine, and metabolic consequences of LAA closure have to be studied in more detail in controlled randomized clinical trials.

Conflict of interest

None declared.

Author contributions

B.S. contributed in the treatment of the patient, data collection and analysis, literature research, and writing and is the corresponding author. D.N. contributed in the treatment of the patient, data collection, and review of the manuscript. C.S. contributed in the literature research, data analysis, and writing.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Video S1. TOE of the LAA with 2 devices (WATCHMAN and Amplatzer Plug III) and a large peri-device leak on colour Doppler echocardiography.
Video S2. TOE (Xplane view) displaying 2 occlusion devices in the LAA (left side), a large mobile LAA thrombus (both sides) and a residual leak (right side).
Video S3. Biatrial view on TOE showing a patent foramen ovale with bidirectional shunting on colour Doppler echocardiography.
Video S4. Biatrial view on TOE demonstrating a right atrial appendage thrombus.
Video S5. Three-dimensional TOE showing 2 occluders in the ostium of the LAA and a large mobile LAA thrombus.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893–2962.
2. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR Jr, PREVAIL and PROTECT AF Investigators. 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J Am Coll Cardiol* 2017; **70**: 2964–2975.
3. Dukkipati SR, Kar S, Holmes DR Jr, Doshi SK, Swarup V, Gibson DN, Maini B, Gordon NT, Main ML, Reddy VY. Device-related thrombus after left atrial appendage closure: incidence, predictors, and outcomes. *Circulation* 2018; **138**: 874–885.
4. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; **61**: 755–759.
5. Johnson WD, Ganjoo AK, Stone CD, Srivyas RC, Howard M. The left atrial appendage: our most lethal human attachment! Surgical implications. *Eur J Cardiothorac Surg* 2000; **17**: 718–722.
6. Stöllberger C, Schneider B, Finsterer J. Elimination of the left atrial appendage to prevent stroke or embolism? Anatomic, physiologic, and pathophysiologic considerations. *Chest* 2003; **124**: 2356–2362.
7. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011; **123**: 2363–2372.
8. Sennesael AL, Larock AS, Devalet B, Mathieux V, Verschuren F, Muschart X, Dalleur O, Dogné JM, Spinewine A. Preventability of serious thromboembolic and bleeding events related to the use of oral anticoagulants: a prospective study. *Br J Clin Pharmacol* 2018; **84**: 1544–1556.
9. Hoit BD, Walsh RA. Regional atrial distensibility. *Am J Physiol* 1992; **262**: H1356–H1360.
10. Hoit BD, Shao Y, Tsai LM, Patel R, Gabel M, Walsh RA. Altered left atrial compliance after atrial appendectomy. Influence on left atrial and ventricular filling. *Circ Res* 1993; **72**: 167–175.
11. Hondo T, Okamoto M, Yamane T, Kawagoe T, Karakawa S, Yamagata T, Matsuura H, Kajiyama G. The role of the left atrial appendage. A volume loading study in open-chest dogs. *Jpn Heart J* 1995; **36**: 225–234.
12. Davis CA 3rd, Rembert JC, Greenfield JCJ. Compliance of left atrium with and without left atrium appendage. *Am J Physiol* 1990; **259**: H1006–H1008.

13. Rodeheffer RJ, Naruse M, Atkinson JB, Naruse K, Burnett JC Jr, Merrill WH, Frist WH, Demura H, Inagami T. Molecular forms of atrial natriuretic factor in normal and failing human myocardium. *Circulation* 1993; **88**: 364–371.
14. Majunke N, Sandri M, Adams V, Daehnert I, Mangner N, Schuler G, Moebius-Winkler S. Atrial and brain natriuretic peptide secretion after percutaneous closure of the left atrial appendage with the WATCHMAN device. *J Invasive Cardiol* 2015; **27**: 448–452.
15. Cruz-Gonzalez I, Palazuelos Molinero J, Valenzuela M, Rada I, Perez-Rivera JA, Arribas Jimenez A, Gabella T, Prieto AB, Martín Polo J, Sánchez PL. Brain natriuretic peptide levels variation after left atrial appendage occlusion. *Catheter Cardiovasc Interv* 2016; **87**: E39–E43.
16. Tzikas A, Holmes DR Jr, Gafoor S, Ruiz CE, Blomström-Lundqvist C, Diener HC, Cappato R, Kar S, Lee RJ, Byrne RA, Ibrahim R, Lakkireddy D, Soliman OI, Nabauer M, Schneider S, Brachmann J, Saver JL, Tiemann K, Sievert H, Camm AJ, Lewalter T. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace* 2017; **19**: 4–15.
17. Granier M, Laugaudin G, Massin F, Cade S, Winum PF, Freitag C, Pasquie JL. Occurrence of incomplete endothelialization causing residual permeability after left atrial appendage closure. *J Invasive Cardiol* 2018; **30**: 245–250.
18. Hornung M, Gafoor S, Id D, Vaskelyte L, Hofmann I, Franke J, Sievert H, Bertog SC. Catheter-based closure of residual leaks after percutaneous occlusion of the left atrial appendage. *Catheter Cardiovasc Interv* 2016; **87**: 1324–1330.
19. Shamim S, Magalski A, Chhatriwalla AK, Allen KB, Huber KC, Main ML. Transesophageal echocardiographic diagnosis of a WATCHMAN left atrial appendage closure device thrombus 10 years following implantation. *Echocardiography* 2017; **34**: 128–130.
20. Luani B, Groscheck T, Genz C, Tanev I, Rauwolf T, Herold J, Medunjanin S, Schmeisser A, Braun-Dullaeus RC. Left atrial enlargement and clinical considerations in patients with or without a residual interatrial shunt after closure of the left atrial appendage with the WATCHMAN™-device. *BMC Cardiovasc Disord* 2017; **17**: 294.
21. Bai R, Horton RP, DI Biase L, Mohanty P, Pump A, Cardinal D, Scallon C, Mohanty S, Santangeli P, Brantes MC, Sanchez J, Burkhardt JD, Zagrodzky JD, Gallinghouse GJ, Natale A. Intraprocedural and long-term incomplete occlusion of the left atrial appendage following placement of the WATCHMAN device: a single center experience. *J Cardiovasc Electrophysiol* 2012; **23**: 455–461.
22. Sattler K, Behnes M, Barth C, Wenke A, Sartorius B, El-Battrawy I, Mashayekhi K, Kuschyk J, Hoffmann U, Papavasiliu T, Fastner C, Baumann S, Lang S, Zhou X, Yücel G, Borggrefe M, Akin I. Occlusion of left atrial appendage affects metabolomic profile: focus on glycolysis, tricarboxylic acid and urea metabolism. *Metabolomics* 2017; **13**: 127.
23. Yücel G, Behnes M, Barth C, Wenke A, Sartorius B, Mashayekhi K, Yazdani B, Bertsch T, Rusnak J, Saleh A, Hoffmann U, Fastner C, Lang S, Zhou X, Sattler K, Borggrefe M, Akin I. Percutaneous closure of left atrial appendage significantly affects lipidome metabolism. *Sci Rep* 2018; **8**: 5894.