

Left Atrial Appendage Isolation in Patients Not Responding to Pulmonary Vein Isolation

Benefit and Risks

Pulmonary vein isolation (PVI) is an effective strategy for patients with paroxysmal atrial fibrillation (AF).¹ However, in patients with persistent AF and long-standing persistent AF, PVI is associated with limited success, with patients not responding to PVI.² Recently, the BELIEF trial (Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Longstanding Persistent Atrial Fibrillation Undergoing Catheter Ablation) showed that an electric isolation of the left atrial (LA) appendage (LAA) in addition to PVI could increase clinical success.³ Although potentially effective, this strategy causes electromechanical dissociation of the LAA and was assumed to be associated with increased risk for LAA thrombus and thromboembolism.⁴ We sought to investigate the incidence of LAA thrombus and thromboembolism and the impact of LAA closure on the prevention of thromboembolic events, in addition to the clinical benefit after left atrial appendage isolation (LAAI).

One hundred sixteen patients with AF or atrial tachycardia and LAAI were prospectively enrolled (LAAI group). LAAI was achieved by PVI, linear lesions, and substrate modifications after a median of 2 failed ablation procedures. The patients were compared with a control group of 116 patients with recurrent AF or atrial tachycardia after ≥ 1 failed AF ablation with PVI, linear lesions, and substrate modifications but without LAAI. The control group was identified by propensity score matching (variables included age, sex, arterial hypertension, diabetes mellitus type II, coronary artery disease, CHA₂DS₂-VASc score, LA diameter, and AF type) from our institutional long-term follow-up database (n=551). All subjects gave written informed consent. The study was approved by the institutional review board and was performed in accordance with the Declaration of Helsinki.

Our ablation strategies have been described in detail before.^{2,5} All patients underwent transesophageal echocardiography before the procedure. LAAI was the result of achieving bidirectional block of an anterior and a mitral isthmus line aiming to treat LA macro-reentrant tachycardia or documented localized reentrant atrial tachycardia originating near the LAA base, or it was the result of extensive ablation of complex fractionated atrial electrograms at the anterior LA and mitral isthmus. LAAI was achieved by linear ablation in 104 patients (90%). In 12 patients (10%), the LAA was isolated during extensive ablation of complex fractionated atrial electrograms at the anterior wall and the LA isthmus.

Lifelong oral anticoagulation (OAC) was strongly recommended to all patients undergoing LAAI. For control group patients, OAC was continued for ≥ 3 months. Afterward, OAC was recommended on the basis of the patient's CHA₂DS₂-VASc score.

ECGs and Holter ECG recordings were performed in our outpatient clinic or by the referring physician on day 1 after procedure; at 1, 3, and 6 months; and at 6-month intervals thereafter. Transesophageal echocardiography within 3 months

Christian-Hendrik Heeger, MD*
Andreas Rillig, MD*
Dominic Geisler, BS
Peter Wohlmuth, PhD
Thomas Fink, MD
Shibu Mathew, MD
Roland Richard Tilz, MD
Bruno Reissmann, MD
Christine Lemes, MD
Tilman Maurer, MD
Francesco Santoro, MD
Osamu Inaba, MD
Christian Sohns, MD
YinHao Huang, MD
Hannes Alessandrini, MD
Inge Dotz, MD
Michael Schlüter, PhD
Andreas Metzner, MD
Karl-Heinz Kuck, MD
Feifan Ouyang, MD

*Drs Heeger and Rillig contributed equally.

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Table. Baseline Characteristics, Echocardiographic Details, and Adverse Events

	Control Group	LAAI Group	P Value
Patients, n	116	116	
Baseline characteristics			
Age, y	66.4±7.3	66.8±8.7	0.999*
Female, n (%)	54 (46.6)	57 (49.1)	0.999*
Congestive heart failure, n (%)	11 (9.5)	9 (7.8)	0.650†
Hypertension, n (%)	69 (59.5)	69 (59.5)	0.999*
Diabetes mellitus type 2, n (%)	9 (7.8)	10 (8.6)	0.999*
Coronary artery disease, n (%)	23 (19.8)	22 (19.0)	0.999*
Previous embolic stroke or TIA, n (%)	12 (10.3)	13 (11.2)	0.999†
CHA ₂ DS ₂ -VASc score	2.2±1.4	2.2±1.4	0.999*
LA diameter, mm	46 (42, 50)	46 (42, 50)	0.999*
Paroxysmal AF, n (%)	40 (34.5)	41 (35.3)	0.999*
Persistent AF, n (%)	46 (39.7)	44 (37.9)	0.788†
Long-standing persistent AF, n (%)	30 (25.9)	31 (26.7)	0.999†
Total procedures, including index, n	2 (1, 2)	3 (2, 4)	<0.001‡
LAAI during the first procedure, n (%)	...	7 (6)	...
LAAI during ablation of linear lesion, n (%)	...	104 (90)	...
LAAI during ablation of complex fractionated atrial electrograms at the LA anterior wall, n (%)	...	12 (10)	...
Echocardiographic details before index procedure assessed by TEE			
LAA morphology, n (%)			
Cactus	33 (28.4)	28 (24.1)	0.551†
Chicken wing	39 (33.6)	44 (37.9)	0.493†
Windsock	21 (18.1)	24 (20.7)	0.624†
Cauliflower	12 (10.3)	14 (12.1)	0.836†
Undetermined	11 (9.5)	6 (5.2)	0.314†
Smoke in LAA	13 (11.2)	14 (12.1)	0.841†
Degree of smoke in LAA (grade)	1 (1, 2)	1.5 (1, 2)	0.666‡
LAA flow velocity, m/s	0.47±0.2	0.42±0.1	0.105‡
Echocardiographic details after index procedure assessed by TEE			
Availability of postprocedural TEE, n (%)	89 (77)	95 (82)	0.418†
Smoke in LAA, n (%)	10 (11.2)	36 (37.8)	<0.0001†
Degree of smoke in LAA	1 (1, 2.8)	3 (2, 3)	0.003‡
LAA flow velocity, m/s	0.50±0.2	0.22±0.2	<0.0001‡
Thrombus formation within LAA, n (%)	2 (2.2)	22 (23.2)	<0.0001†
Appropriate OAC at time of detected thrombus, n (%)	1 (50)	20 (91)	0.239†
Adverse events			
Follow-up duration, y	4.3 (3.7, 5.6)	4.0 (2.5, 6.4)	0.222‡
Thromboembolism (stroke or TIA), n (%)	3 (2.6)	17 (14.7)	0.002†
Embolic stroke, n (%)	1 (0.9)	15 (12.9)	...
TIA, n (%)	2 (1.7)	2 (1.7)	...
Patients with 2 thromboembolic events, n (%)	0 (0)	3 (2.6)	0.247†
Time point of thromboembolism, mo	25 (18, 55)	16 (7, 47)	0.461‡
Thromboembolism under appropriate OAC, n (%)	1 (33.3)	15 (88)	0.088†
OAC: vitamin K antagonists (INR, 2–3)	1	10	...
OAC: rivaroxaban	0	4	...

(Continued)

Table. Continued

	Control Group	LAAI Group	P Value
OAC: apixaban	0	0	...
OAC: dabigatran	0	1	...
LAA thrombus formation, n (%)	2/89 (2.2)	22/95 (23.2)	<0.0001†
LAA thrombus under appropriate OAC, n (%)	1 (50)	20 (91)	0.330†
Patients with thromboembolism and LAA thrombus, n (%)	0 (0)	6 (35)	0.554†
Combined end point, n (%)			
LAA thrombus and thromboembolism	5 (4.3)	33 (28.4)	<0.0001†
Thromboembolism with/without LAA closure			
Patients with LAA closure (n=48)	...	2 (4.2)	...
Patients without LAA closure (n=68)	...	15 (22.1)	0.007†

Values are mean±SD, median (first, third quartile) as appropriate. Propensity score matching with a test of no regression was based on the following variables: age, sex, arterial hypertension, diabetes mellitus type II, coronary artery disease, CHA₂DS₂-VASc score, LA diameter, and type of AF. AF indicates atrial fibrillation; INR, international normalized ratio; LA, left atrial; LAA, left atrial appendage; LAAI, left atrial appendage isolation; OAC, oral anticoagulation; TEE, transesophageal echocardiography; and TIA, transient ischemic attack. *Paroxysmal AF. Further comparisons were based on †Fisher exact test and ‡Mann-Whitney U test. All P values were 2 sided, and a value of P<0.05 was considered significant. All calculations were performed with the statistical analysis software R (R Core Team, 2018).

after the procedure was recommended to assess LAA thrombus.

Postprocedural LAA thrombus was detected in 22 of 95 patients (23.2%) undergoing LAAI and in 2 of 89 control group patients (2.2%; $P<0.0001$; Table).

During a median follow-up of 4.0 years (LAAI group) and 4.3 years (control group; $P=0.222$), a total of 17 patients undergoing LAAI (14.7%) and 3 control group patients (2.6%) experienced a cerebral thromboembolic event ($P=0.002$).

Endocardial LAA closure was recommended to all patients and performed in 48 (41.4%). Thromboembolic events occurred in 2 of 48 patients (4.2%) with LAA closure and 15 of 68 patients (22.1%) without LAA closure ($P=0.007$). In patients with LAA closure, no LAA thrombus was found on transesophageal echocardiography at day 1 before LAA closure, and OAC was stopped, yet the periprocedural guiding transesophageal echocardiography detected LAA thrombus in 2 patients.

Finally, the 4-year arrhythmia-free survival rate was maintained at 48.6% (95% CI, 40.0–57.2) in the LAAI group and 37.4% (95% CI, 30.2–44.6) in the control group ($P=0.02$).

Loss of LAA mechanical function after LAAI can theoretically increase thromboembolic risk; therefore, it seems reasonable to recommend lifelong OAC regardless of the CHA₂DS₂-VASc score.⁴ Because 91% of patients with LAA thrombus were on sufficient OAC, this strategy seems not to be sufficient to prevent LAA thrombus and thromboembolic events. LAA closure after LAAI may be a viable option to reduce the risk of thromboembolism without the necessity to intensified OAC and its potential consequences.

Similar to the BELIEF trial, we demonstrated that LAAI in addition to PVI improves clinical success of patients with AF not responding to PVI.³ However, in contrast to the low rate of LAA thrombus (1.8%) and thromboem-

bolism (0%), we observed a very high incidence of both despite appropriate OAC. Although different ablation strategies (wide-area versus circular LAAI) might be a possible explanation for this discrepancy, the underlying mechanism of electric LAAI with consecutive loss of mechanical contraction should occur with both techniques. The observation of similar LAA flow velocity and smoke before ablation in both groups and significant differences afterward supports the mechanism of LAA thrombus formation by local stasis after LAAI.

Wide-area LAAI might be an additional treatment option for patients with AF not responding to PVI. However, a high incidence of thromboembolic events and LAA thrombus was observed despite sufficient OAC, which is limiting the meager clinical benefit. Although the risk of thromboembolic events can be significantly reduced with LAA closure, this potential risk should be taken into consideration by all electrophysiologists in clinical practice.

ARTICLE INFORMATION

Data Sharing: The data will not be available to other researchers.

Correspondence

Feifan Ouyang, MD, Asklepios Klinik St. Georg, Department of Cardiology, Lohmühlenstr. 5, 20099 Hamburg, Germany; or Feifan Ouyang, MD, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangzhou 510120, China. Email ouyangfeifan@gmail.com

Affiliations

Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany (C.-H.K., A.R., D.G., T.F., S.M., R.R.T., B.R., C.L., T.M., F.S., O.I., Y.H., H.A., I.D., M.S., A.M., K.-H.K., F.O.). University Heart Center Luebeck, Medical Clinic II (Department of Cardiology, Angiology and Intensive Care Medicine), Division of Electrophysiology, University Hospital Schleswig-Holstein, Germany (C.-H.K., T.F., R.R.T.). Asklepios Proresearch, Hamburg, Germany (P.W.). Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangzhou, China (F.O.).

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