

FOCUS ISSUE: STRUCTURAL HEART DISEASE

Clinical Research

Transcatheter Patch Occlusion of the Left Atrial Appendage Using Surgical Adhesives in High-Risk Patients With Atrial Fibrillation

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- Objectives** The efficacy of left atrial appendage (LAA) occlusion using the Transcatheter Patch (TP) (Custom Medical Devices, Athens, Greece) in conjunction with surgical adhesives was assessed.
- Background** The TP is a bioabsorbable device that can be adjusted for the shape and size of the LAA without the risk of perforation. It is attached by a surgical adhesive and is released in 45 min.
- Methods** Occlusion of the LAA was performed in 20 high-risk patients, 59 to 89 years of age, with atrial fibrillation. A 2-stage polyethylene glycol surgical adhesive was applied to the distal half of the device. Activation of the adhesive was achieved by direct injection of alkaline solution. Fluoroscopy and transesophageal echocardiography only were used for device placement in 17 patients. In 3 patients, angiography was used as well. Follow-up transesophageal echocardiography was performed upon discharge.
- Results** The procedure was successful in 17 cases. In the 3 patients in whom angiography was performed, the patch did not attach and was retrieved. In 1 case, the patch was placed beyond the mouth of the appendage, resulting in a residual opening. There was further improvement of the occlusion rate on the follow-up transesophageal echocardiography. There was 1 complication related to the procedure, namely, thrombus was released from the long sheath in the left atrium upon withdrawal and required treatment to be dissolved. No recurrent strokes were reported.
- Conclusions** Occlusion of the LAA by the TP is feasible and effective in most patients with atrial fibrillation at high risk for embolic stroke. Angiography before placement probably affects patch adhesion and is contraindicated. (J Am Coll Cardiol 2011;58:2236–40) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation is the most common cause of embolic stroke in cases with nonvalvular disease (1). Transesophageal echocardiography (TEE) has shown that the left atrial appendage (LAA) is the most common site for thrombus formation, and criteria have been defined for patients who are at high risk for thrombosis (2). Warfarin treatment has been the traditional method for stroke prophylaxis in patients with atrial fibrillation; however, there are several problems related to efficacy, side effects, and compliance with treatment (3). Non-warfarin medications show prom-

ise, but they require long-term evaluation (4). Surgical and thoracoscopic obliterations of the LAA have been used, but they are associated with known surgical morbidity (5,6). Metal devices have also been used successfully for the occlusion of the LAA, but concerns remain regarding thrombogenicity, risk for perforation, and embolization (7). Furthermore, because the size of the appendage varies, several device sizes are required for the same procedure (8). LAA obliteration by the Transcatheter Patch (TP) (Custom Medical Devices, Athens, Greece) could be an effective alternative, as it potentially reduces the long-term risks of perforation, thromboembolism, and embolization. Additionally, the patch is balloon deliverable and can conform to all or most LAAs, necessitating only a single size device.

Effectiveness and safety have been demonstrated in TP obliteration of the LAA in piglets using accelerated fibrin formation principles and surgical adhesives (9). Use of

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Manuscript received April 19, 2011; revised manuscript received July 20, 2011, accepted August 2, 2011.

surgical adhesives appeared very attractive in animal studies as the patch could be released in as early as 15 min. The purpose of this study was to assess the effectiveness of TP obliteration of the LAA using the surgical adhesives method in patients with atrial fibrillation at high risk with warfarin treatment.

Methods

LAA occlusion was performed in 20 high-risk patients, 59 to 89 years of age, with idiopathic atrial fibrillation. Informed consent was obtained from each patient. All patients had a CHADS₂ score >3 (clinical prediction rule for estimating the risk of stroke: C = congestive heart failure, H = hypertension, A = age, D = diabetes, S₂ = prior stroke or transient ischemic attack). Previous stroke existed in 8, intolerance or contraindication to warfarin in 10, bleeding ulcer in 9, congestive heart failure in 5, diabetes in 5, and old LAA thrombus in 3. There was also a single patient who was recently converted to sinus rhythm by ablation, but was unable to take warfarin. Further patient information can be seen in Table 1.

Fluoroscopy and TEE were used throughout the procedure. The atrial septum was perforated using standard transeptal puncture techniques. A multipurpose catheter was advanced in the LAA, and the position, size, and shape of the appendage were confirmed by TEE in all patients and by angiography in 3 patients. A 0.035-inch exchange wire was positioned deeply in the appendage, and a 13-F long Mullins sheath (Cook, Bloomington, Indiana) was advanced to the appendage over the guidewire.

Transcatheter patch. The TP, shown in Figure 1, is a frameless, balloon-deliverable device used for the occlusion

of heart defects. The patches are tailored from polyurethane foam (Foamex, Media, Pennsylvania). The supporting balloon is made from Latex (NuMED, Hopkinton, New York) and is inflated to diameters of 15 to 25 mm by diluted contrast. A 2-mm nylon loop is sutured at the bottom of the patch, to which a double nylon thread is connected for retrieval purposes.

Surgical adhesive. A pH-activated polyethylene glycol based surgical adhesive is used (Baxter, Deerfield, Illinois), and is prepared as follows. The polyethylene glycol powder is diluted in acidic solution A, provided in the packaging. Approximately 1 to 2 ml of the dilution is applied on the distal half of the patch. The adhesive is inactive under acidic conditions and can thus be advanced through the sheath to the LAA. Activation is accomplished by exposing the adhesive to alkaline solution B after the device has been positioned and inflated.

Patch delivery. The device complex is advanced through the long sheath over the guidewire into the LAA. The balloon is inflated with dilute contrast until it stretches the LAA (3 to 10 ml of injectable volume corresponds to 14 to 25 mm patch diameter). Subsequently, alkaline solution B is injected through the central lumen of the catheter. The balloon/patch position is confirmed by fluoroscopy and TEE. The supportive balloon catheter is removed 45 min after surgical adhesive activation according to the following procedure: the balloon is deflated, and the catheter assembly is retracted through the introducing sheath with the tip of

Abbreviations and Acronyms

LAA = left atrial appendage
TP = Transcatheter Patch
TEE = transesophageal echocardiogram

Table 1 Patient Information

Patient #	Age (Yrs)	LAA (mm)	TP (mm)	Release (min)	Result	Indication/Comment
1	79	20	21	45	FO	Bleeding ulcer
2	71	18	20	45	FO	Peptic system bleeding
3	59	19	21	45	FO	Hemorrhagic stroke, LA thrombus
4	62	16	29	45	TS	Ischemic stroke, LA thrombus
5	75	23	24	45	—	Patch not attached, angiography
6	89	17	29	45	FO	Bleeding ulcer
7	70	20	21	45	PO	Previous stroke, gastric ulcer
8	76	24	25	45	FO	Stroke on warfarin
9	64	14	20	45	FO	Heart failure, diabetes, warfarin con.
10	75	23	24	45	FO	Previous stroke, warfarin con.
11	75	18	20	45	FO	Hypertension, diabetes, warfarin con.
12	74	17	19	45	FO	Hypertension, diabetes, warfarin con.
13	75	15	16	45	FO	Warfarin con.
14	80	21	23	45	FO	Bleeding disorder
15	70	18	20	45	FO	Previous stroke
16	75	20	22	45	FO	Previous stroke, hypertension
17	75	24	25	45	—	No attachment, angiography
18	82	21	23	45	—	No attachment, angiography, bleeding
19	80	20	22	45	FO	Long sheath thrombus, anticoagulation
20	75	19	21	45	FO	Warfarin con.

con. = contraindicated; FO = full occlusion; LA = left atrium; LAA = left atrial appendage; PO = partial occlusion; TP = Transcatheter Patch; TS = trivial shunt.

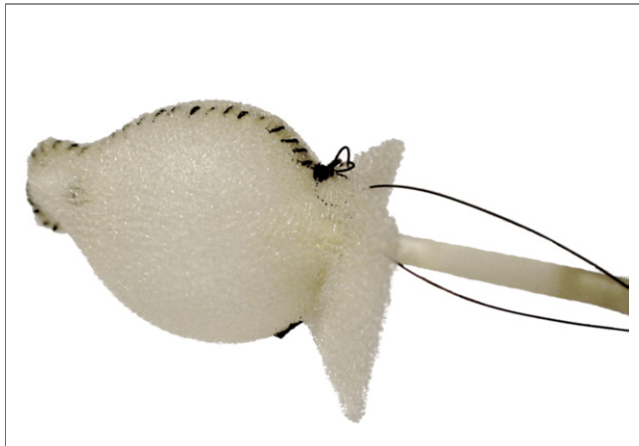


Figure 1 Transcatheter Patch

The Transcatheter Patch device for occlusion of heart defects is tailored from polyurethane foam. Diluted contrast inflates the supporting balloon to diameters of 15 to 25 mm. A 2-mm nylon loop is sutured at the bottom of the patch, and a double nylon thread is connected for retrieval purposes.

the sheath held against the patch; the position and stability of the patch is confirmed by pulling lightly on the retrieval thread under echocardiography. If the result is satisfactory, the patch is released by removing the double nylon thread.

Diagnostic angiography was performed in 3 cases directly before device implantation as well as during the 45-min waiting period before patch release. Transesophageal echocardiography was used to evaluate the result after balloon catheter withdrawal and on follow-up. Images depicting a LAA before and after occlusion can be seen in Figures 2 and 3. Cephalosporins were given prophylactically intravenously. The patient was observed overnight in the intensive care unit, and an aspirin regimen (300 mg daily) was started within 24 h.

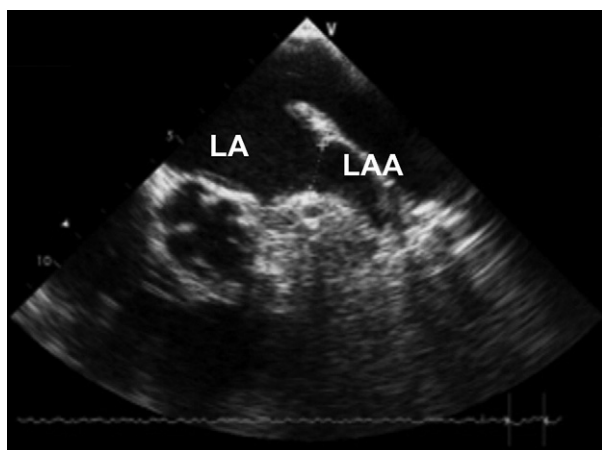


Figure 2 LAA Before Occlusion

LA = left atrium; LAA = left atrial appendage.

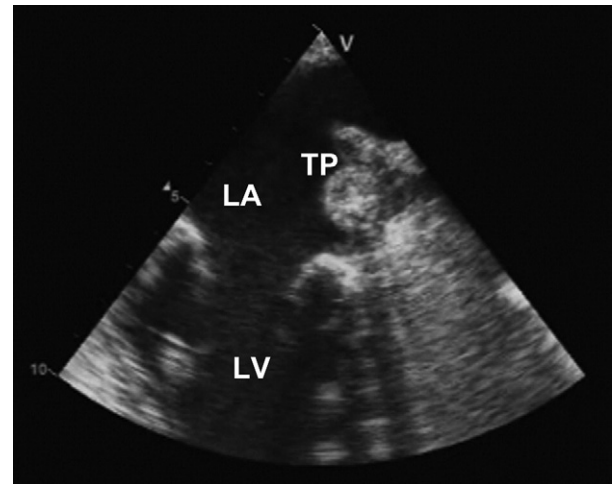


Figure 3 LAA After TP Occlusion

For more information on this case, please see the Online Video. LA = left atrium; LAA = left atrial appendage; LV = left ventricle; TP = Transcatheter Patch.

Follow-up. Follow-up TEE was performed on all patients 24 h after device implantation. Clinical follow-up was obtained by the primary physician for at least 1 year. Additional TEEs were obtained in selected cases.

Results

The LAA was entered after successful transeptal puncture in all patients. Measurements of the appendage mouth size revealed a range from 15 to 24 mm in diameter among patients. In the 17 procedures that were carried out without angiography, TP placement was successful. In the 3 cases in which angiography was performed, the patch was not attached after 45 min and was retrieved through the introducing sheath. All other patients had their appendages occluded. In 1 case, the patch was placed beyond the mouth of the appendage, resulting in a residual opening. The occlusion result improved significantly within 24 h as assessed by the follow-up TEE. In 1 case, there was some uncertainty related to the stability of the patch, and vigorous test pulling was used for confirmation. This case presented a complication directly after device release in that thrombus was extracted from the tip of the long sheath. The thrombus required aggressive treatment and was resolved within 1 week; the atrial appendage remained fully occluded. No recurrent strokes or bleeding complications were reported.

Discussion

The TP has been shown to be effective in the occlusion of a variety of heart defects including atrial septal defect, ventricular septal defect, patent ductus arteriosus, and patent foramen ovale (10–12). Occlusion of the LAA has the potential of being an ideal application for the TP, given

the geometric conformity of the device and the appendage. The TP is made from porous polyurethane, which normally attaches to the cardiac tissue by fibrin formation within 48 h (13). In the present study, the attachment time was shortened through the use of a pH-activated surgical adhesive. Since balloon inflation effectively seals the LAA, solution B could be injected to cause a localized pH shift distally to the balloon. That led to a further reduction in the attachment time beyond that possible using the surgical adhesive technique in other lesions (14). On the basis of the animal studies mentioned previously, an attachment time closer to 15 min may be possible, but further work is needed to confirm its safety. The adhesive has been used extensively after cardiac or peripheral vascular surgery, where mixing of the components is performed simultaneously (15). It is bioabsorbable and is eliminated from the body within 1 month. An additional property of the adhesive is that it increases in volume after placement owing to water absorption; this may explain the improvement in appendage occlusion after 24 h.

In all 3 failed procedures in this study, diagnostic angiography had been performed. We speculate that the contrast medium may have interfered with the adhesion by causing a change in pH. Consequently, use of angiography may be contraindicated with this method, but further *in vitro* studies are required to confirm this assertion. An additional drawback of the method is the inconvenience related to the 45-min waiting period, although this is significantly less than with other lesions. The single complication of acute thrombus that was observed in this study was likely related to vigorous operator manipulations. As we have not encountered this problem previously, we expect that it will not occur if such manipulations are avoided.

Study limitations. A limitation of this study was that the appendages used were of relatively small size (<25 mm). Hence, the effectiveness of the method remains unproven in larger sizes, although we expect an improvement over atrial septal defect occlusion for which the method is only effective for defects <25 mm (14). The most recent model of the TP, the Immediate Release Patch, may offer solutions to these problems as fixation within the appendage is immediate by expansion; adhesion to tissue takes place several hours later through fibrin formation (16). Additionally, the drawbacks related to safe attachment time, long sheath thrombus formation, and contraindication to angiography should be eliminated.

Conclusions

In this study, we have shown that LAA occlusion using the TP in conjunction with surgical adhesives is feasible and safe in most cases. Neither stroke nor thrombogenicity was reported on follow-up, but the study was not designed to prove noninferiority to other treatments. Despite this drawback, it is reasonable to assume that the long-term results of the TP used in stroke prevention should be similar to those

for the Watchman device and not inferior to warfarin (17). Furthermore, the fast endothelialization of the wireless patch prevents the need for anticoagulant treatment, which is used for a few days after Watchman device implantation. In conclusion, the TP, used with surgical adhesives, can offer an alternative to LAA occlusion with metal devices.

Acknowledgments

The authors would like to thank Dr. Y. Karpenko (Odessa, Ukraine) and Dr. S. Rokas (Athens, Greece) for referring some of the patients in the study. The TP was used off-label for LAA occlusion. Additionally, an off-label, 2-stage activation was used with the polyethylene glycol adhesive to allow TP introduction and placement.

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REFERENCES

1. Wolf PA, Dawber TR, Thomas HE Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;28:973–7.
2. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. *Ann Intern Med* 1998;128:639–47.
3. Atrial Fibrillation Investigators. Atrial Fibrillation, Anticoagulation Study, Boston Area Anticoagulation Trial for Atrial Fibrillation Study, Canadian Atrial Fibrillation Anticoagulation Study, Stroke Prevention in Atrial Fibrillation Study, Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–57.
4. Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* 2010;159:331–9.
5. Madden JL. Resection of the left auricular appendix. *JAMA* 1949; 140:769–72.
6. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;61:755–9.
7. Nakai T, Lesh MD, Gerstenfeld EP, Virmani R, Jones R, Lee RJ. Percutaneous left atrial appendage occlusion (PLAATO) for preventing cardioembolism: first experience in canine model. *Circulation* 2002;105:2217–22.
8. Sievert H, Lesh MD, Trepels T, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation* 2002;105:1887–9.
9. Sideris EB, Toumanides S, Stylianos R, Macuil B, Mouloupoulos S. Transcatheter patch obliteration of the left atrial appendage: experimental validation and early clinical experience. *J Am Coll Cardiol* 2006;47:1B.
10. Sideris EB, Toumanides S, Macuil B, et al. Transcatheter patch correction of secundum atrial septal defects. *Am J Cardiol* 2002;89:1082–6.
11. Sideris EB, Macuil B, Varvarenko V, Toumanides S. Transcatheter patch occlusion of perimembranous ventricular septal defects. *Am J Cardiol* 2005;95:1518–21.
12. Sideris B, Coulson JD, Sideris EB. Transcatheter Patch Device. In: Hijazi ZM, Feldman T, Al-Qbani A, editors. *Transcatheter Closure of ASDs and PFOs: A Comprehensive Assessment*. Minneapolis, MN: Cardiotext Publishing, 2010:373–82.

13. Sideris EB, Sideris CE, Stamatelopoulos SF, Mouloupoulos SD. Transcatheter patch occlusion of experimental atrial septal defects. *Catheter Cardiovasc Interv* 2002;57:404–7.
14. Calachanis M, Zamora R, Coulson J, Toumanides S, Sideris E. Effectiveness of transcatheter patch release with surgical adhesives in the occlusion of heart defects. *Cardiology Young* 2007;17:31–2.
15. Hagberg RC, Safi HJ, Sabik J, Conte J, Block JE. Improved intraoperative management of anastomotic bleeding during aortic reconstruction: results of a randomized controlled trial. *Am Surg* 2004;70:307–11.
16. Sideris B, Sideris E, Calachanis M, Papantoniou V, Mouloupoulos S. The immediate release patch in the correction of experimental atrial septal defects. *Catheter Cardiovasc Interv* 2010;76:572–7.
17. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;374:534–42.

Key Words: atrial fibrillation ■ left atrial appendage occlusion ■ transcatheter patch.

 **APPENDIX**

For a supplementary video, please see the online version of this article.