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Closure of foramen ovale triggered by injury to tunnel surfaces of septum primum and secundum

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Abstract

Introduction We investigated the feasibility to proactively stimulate subsequent closure of a patent foramen ovale (PFO) by injuring (mechanical trauma or radiofrequency [RF] energy) the opposing surfaces of the septum primum (SP) and septum secundum (SS).

Methods *1. Mechanical Injury*: The interatrial septum of patients who underwent multiple left atrial (LA) ablations over 6 years, where a PFO was used for LA access, were examined. Patients whose PFO was absent during a later procedure were identified. Eleven patients with LA accessed via a PFO also underwent subsequent LA procedures. *2. Ablation*: Ten patients undergoing ablation for drug-resistant atrial fibrillation (AF), who also had a PFO, were studied. RF delivery was extended along the upper SP. Transthoracic echocardiogram (TTE) bubble study was repeated *after* 3 months.

Results *1. Mechanical Injury*: Seven were male with a mean age of 58.3 ± 9.99. LA size was 42.73 ± 3.52 mm. The mean left ventricular ejection fraction (EF) was 62 ± 7.4%. During the repeat procedure, in 4 patients, the PFO could not be visualized and the fossa ovalis (FO) was punctured. The fourth patient had three procedures. During the second procedure the PFO was accessed, but with difficulty. During the third procedure, it was no longer present. All four patients had subsequent TTE showing no PFO. *2. Ablation:* Seven were male with a mean age of 61.1 ± 9.8 years. The mean EF and LA diameters were 55 ± 5% and 4.4 ± 0.8 cm respectively. The mean RF time was 5.4 ± 2.2 min. At 3 months, 9 patients out of 10 showed no interatrial communication.

Conclusion Injury of tunnel surfaces of the SP and SS by mechanical trauma or ablation can fuse the foramen ovale.

Keywords Patent foramen ovale · Injury · Fusion · Adhesions

1 Background

A patent foramen ovale (PFO) is a communication across the interatrial septum between a nonadherent septum primum (SP) and septum secundum (SS). Normally present in fetal life, it closes in approximately 75% of adults. When present, it occurs equally among both sexes, decreasing in prevalence with advancing age [1]. It is considered to be a risk factor for several serious clinical entities, including strokes from paradoxical emboli, decompression sickness, certain migraines, and complications of pulmonary embolism [2, 3].

The PFO has been long suspected of playing an important role in the genesis of cryptogenic stroke. Recent randomized trials in patients who have a PFO and an embolic stroke, comparing closure with anticoagulation or antiplatelet therapy, have convincingly implicated the PFO of playing a causative role [4–6]. Consequently, the structure/anatomical entity has received markedly increased attention.

The association of a PFO with these clinical problems has led to the development of techniques to achieve closure with permanently implanted devices using multiple technologies and techniques. Device closures of PFOs might be associated with complications in 2 to 20% of patients, including device

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embolization, air embolism, device fracture, pericardial effusion, aortic laceration, residual shunt, endocarditis, and thrombus formation on the device surface [7–11]. A permanently implanted device might also prevent future access to the LA for procedures such as AF ablations. Recent studies show that it is possible to achieve PFO closure without a permanently implanted prosthetic device. These strategies use energy application to seal the PFO closed, and success has been demonstrated in both human and porcine models, although with modest efficacy [12, 13]. Closing a PFO without leaving any foreign material behind is appealing, especially because it might decrease the various acute and chronic risks associated with a chronic implant.

Several years ago, we described an anatomical entity termed left atrial septal pouch (LASP) [14]. This structure provides insights about how adhesions form between the adjacent surfaces of the SP and SS and thus result in the closure of a foramen ovale (FO). The lessons learned from this autopsy study formed the basis for the current project. In some PFO patients with persistent atrial fibrillation (AF) undergoing ablation by our group, energy application was performed along the upper portion of the tunnel surface of the SP to increase the success rates of the procedure. During a subsequent procedure in these patients, a PFO was now noted to be absent. Based on the observation of the LASP, and on findings in patients undergoing ablation procedures, we speculated that it may be possible to proactively stimulate delayed closure of a PFO by injuring (mechanical trauma or radiofrequency (RF) energy) the opposing surfaces of the SP and SS. By doing so, we also attempted to mimic the natural history of PFO closure.

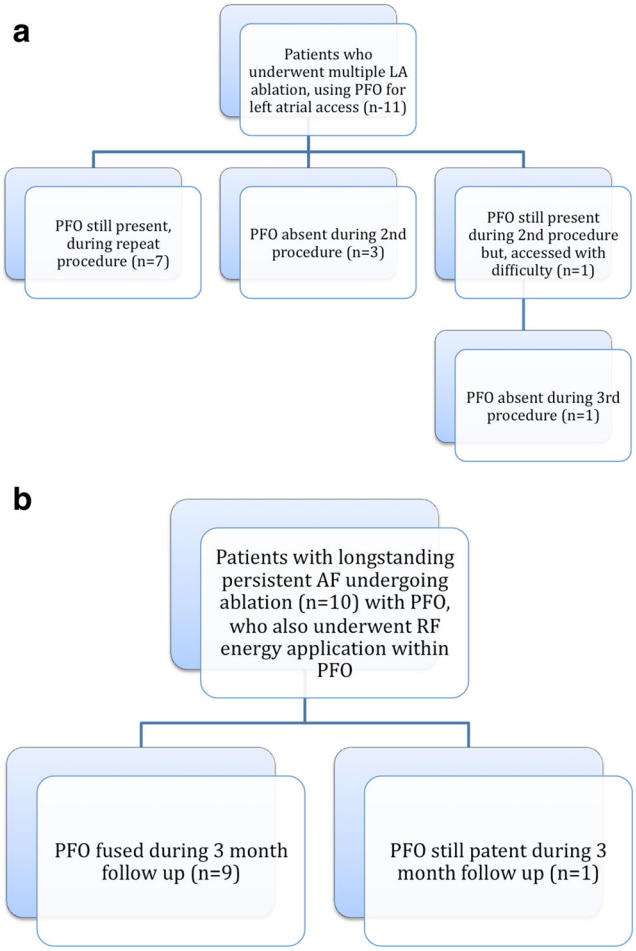

Fig. 1 **a** Flow diagram illustrating sequence of analysis in the mechanical injury subgroup. **b** Flow diagram illustrating study sequence in patients undergoing foramen ovale ablation

2 Methods

2.1 Mechanical injury subgroup

Between 2000 and 2006, patients who had more than one LA ablation procedure in two separate institutions (Henry Ford Hospital, Detroit, MI; University of California Irvine Medical Center, Orange, CA) by the same operator were reviewed. Among these, we selected those who had PFO demonstrated and used for LA access. We then identified patients whose PFO was found to be absent during a later procedure. We found 11 patients with PFO used for LA access who also underwent subsequent LA procedures. The arrhythmias targeted included AF, left atrial flutter, and orthodromic reciprocating tachycardias. Some had the procedure performed with conscious sedation while others received general anesthesia. None performed a Valsalva maneuver during the procedure. The sheath advanced into the LA included an 8-French SL1 sheath or a Mullins Sheath (St. Jude, Minnetonka, MN). The sequence of events and analysis is illustrated in the form of a flow diagram in Fig. 1a.

2.2 Radiofrequency injury subgroup

Ten patients undergoing catheter ablation for persistent drug-resistant AF at St. David's Medical Center, Austin, TX, were included in this study. All patients had a transthoracic echo (TTE) with a bubble study. In addition, intracardiac echo (ICE) examination with pulse, continuous, and color Doppler was performed. The procedures were performed with conscious sedation and therefore, patients were capable of performing a Valsalva procedure during the study. All patients showed a PFO during the baseline echo examination. RF energy delivery was extended along the upper edge of the SP guided by ICE imaging via a 3.5-mm open irrigated ablation catheter. It is possible that in the process of doing so, the tunnel surface of the SS that was immediately adjacent could also have been ablated. ICE was repeated and a second agitated saline study with Valsalva was done immediately following pulmonary vein antral isolation (PVAI) after the transseptal sheaths were withdrawn from the LA into the right atrium. Three months

later, a TTE with bubble study was repeated. A separate informed consent was obtained for the investigational protocol and patient data was prospectively collected in our database after obtaining IRB approval. The study sequence is illustrated in the form of a flow diagram in Fig. 1b.

3 Results

3.1 Mechanical injury subgroup

A typical ICE image example of a sheath and ablation catheter passing from the RA to the LA through a PFO is displayed in Fig. 2a. Of the 11 patients in this "mechanical injury subgroup," seven were males with a mean age of 58.3 ± 9.99. The arrhythmias targeted included AF, atrial flutter, and orthodromic reciprocating tachycardias due to left-sided bypass tracts. The LA size was 42.73 ± 3.52 mm. The mean LV ejection fraction was 62 ± 7.4%.

In the 11 patients undergoing a LA ablation where the chamber was accessed via a PFO, the maneuver of advancing the sheath, ablation, and mapping catheters was performed by the same operator in all patients. When these patients presented for a repeat procedure, in 3 patients, the FO appeared to have fused and a probe could no longer be passed into the LA. This maneuver of trying to access the PFO and the LA was again performed by the same operator who performed the initial ablation procedure. In these patients, a transseptal puncture was performed. A fourth patient underwent three procedures. During the second procedure, a PFO was still present but, unlike the first procedure where the LA could be assessed easily, the chamber was now accessed with some difficulty. During the third procedure, the chamber could not be accessed at all and the PFO had closed. In addition to fluoroscopy in multiple views, the procedure was assisted by ICE in some patients, along with pressure manometry, contrast infusion, color Doppler, and injection of agitated saline.

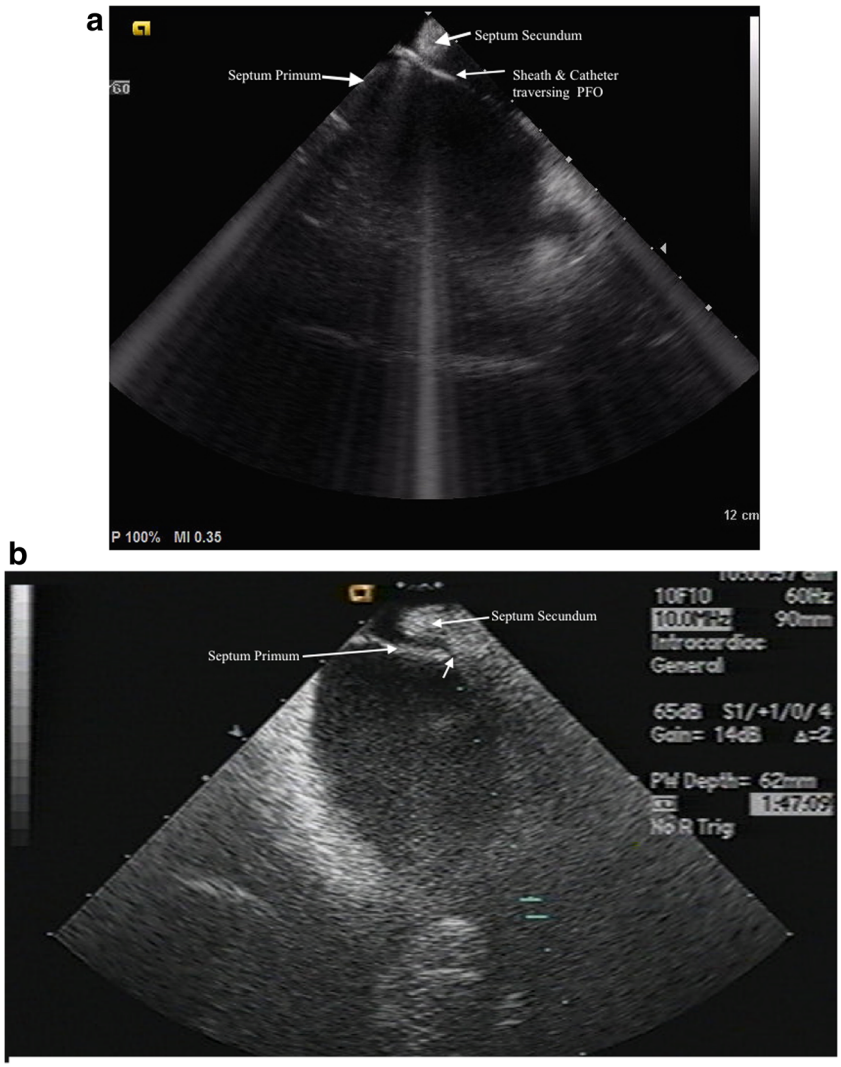

Fig. 2 **a** Intracardiac echo image illustrating example of a sheath and ablation catheter passing from the right to the left atrium through a patent foramen ovale. **b** This image was recorded during a repeat procedure in a patient who had a prior ablation attempted in the left atrium with the chamber accessed via a PFO. During the repeat procedure, a catheter could not be passed through the PFO. The intracardiac echo images suggested that secondary to the mechanical trauma, adhesions had formed at the cranial portion of the zone of overlap (oblique white arrow), with a resulting pouch that could be accessed from the right atrium

An ICE image recorded during a repeat procedure in a patient who had a prior LA ablation with the chamber accessed via a PFO is shown in Fig. 2b. In this patient, during the repeat procedure, a catheter now could not be passed through the PFO. The image suggests that adhesions had formed at the cranial portion of the zone of overlap (oblique white arrow), with a resulting pouch that could be accessed from the RA. It was possible to advance the catheter into the pouch that had been created but not further into the LA. We do not have imaging data on the other 3 patients regarding precisely where fusion occurred along the zone of overlap as the PFO closed. The sheath advanced in all patients was 8 French in diameter and the catheter was 7 French in diameter. Whether a single or multiple sheaths and catheters were introduced through the PFO, these data were not recorded. These were longer procedures (> 2.5 h), suggesting that the duration of the procedures with repeated manipulation of the sheaths may have significantly injured the surfaces of the SP and SS. One patient had three procedures. During the second procedure, the PFO was present, but could be accessed with some difficulty. It was only during the third procedure that it was seen to be no longer present. All four patients had subsequent TTE showing no evidence for PFO. The time between ablation procedures ranged from 3 months to 3 years. To our knowledge, no patient had an atrial septal aneurysm. We did not measure the size of the PFO in any patient.

3.2 Radiofrequency injury subgroup

Figure 3a shows the ICE image of a typical patient in the RF injury subgroup with obvious separation between the SP and SS, undergoing catheter ablation of AF. Access to the LA cavity was obtained via a transseptal puncture of the interatrial septum. This group consisted of patients with persistent long-

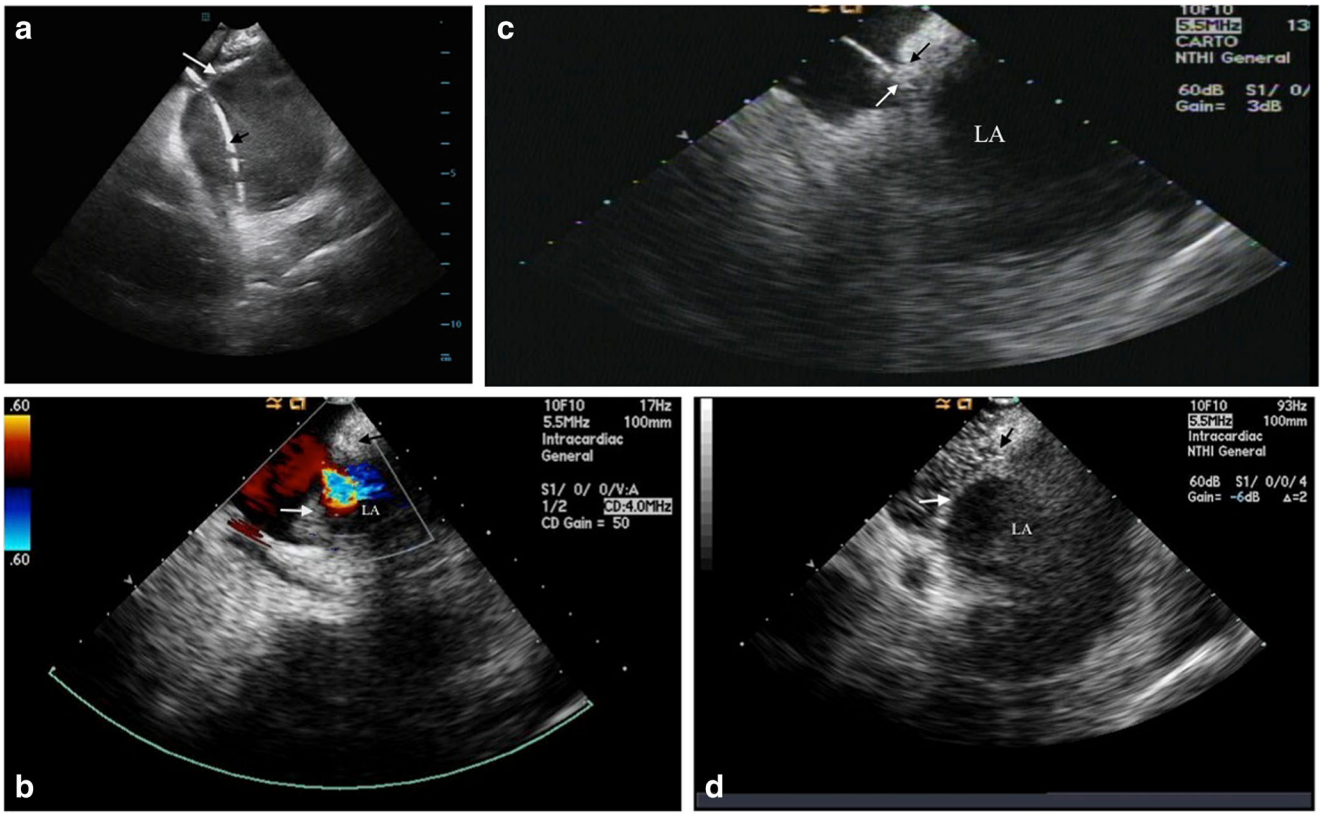

Fig. 3 **a** Intracardiac echo image of a patient with a patent foramen ovale undergoing a catheter ablation of atrial fibrillation. Obvious absence of fusion between the septum primum and secundum can be seen. Access to the left atrial cavity was obtained via a transseptal puncture of the septum primum (white arrow). The ablation catheter is visualized in the left atrial cavity (black arrow). **b** Intracardiac echo image of a patient with a patent foramen ovale undergoing a catheter ablation of atrial fibrillation. Color Doppler recordings obtained during a Valsalva maneuver demonstrate blood flow from right to the left atrium through the PFO are shown. The black arrow is placed over the septum secundum while the white arrow points to the septum primum. **c** Intracardiac echo image of a patient with a patent foramen ovale undergoing a catheter ablation of atrial fibrillation. In addition to undergoing a pulmonary vein antral isolation, this patient also had ablation performed of the tunnel surface of the septum primum along the zone of overlap. The black arrow is placed over the septum secundum while the white arrow points to the ablation catheter. The image was recorded after completion of ablation of the septum primum as the catheter tip was dragged through the tunnel and into the right atrium. **d** Intracardiac echo image of a patient with a patent foramen ovale who underwent a prior catheter ablation of atrial fibrillation as well as a catheter ablation of a PFO. The image was recorded after injection of agitated saline and during a Valsalva maneuver. Possibly due to fusion between the septum primum (white arrow) and secundum (black arrow), there is no flow of agitated saline into the left atrium. This patient previously had a PFO with demonstrable right to left shunting

standing drug-refractory AF. Of the 10 patients in this "Radiofrequency injury subgroup," seven were males with a mean age of 61.1 ± 9.8 years. Initially, in an attempt to improve the success rates of the procedure, ablating the SP was part of our strategy to ablate more of the LA than to just achieve PVAI. The primary intention initially was not to achieve the closure of the FO. Based on preliminary observations of tunnel ablation fusing the PFO, a prospective 10-patient study was then performed.

A typical ICE image with color Doppler recordings of a patient with a PFO undergoing AF ablation is shown in Fig. 3B. Recordings obtained during a Valsalva maneuver demonstrate blood flow from the RA to the LA through the PFO. The black arrow is placed over the SS while the white arrow points to the SP. Conscious sedation was light enough in these patients to allow for the Valsalva maneuver to be performed.

In the RF injury group, the mean ejection fraction and LA diameter were 55 ± 5% and 4.4 ± 0.8 cm respectively. The mean RF time along the PFO was 5.4 ± 2.2 min. The power varied between 40 and 50 W, which is the standard practice for our group. At the time of the study, contact force sensing was not available. While we did not document fluoroscopy times, we largely used ICE to visualize the PFO and to help place catheters within the tunnel. We do not believe that closing PFOs with RF injury resulted in significantly increased radiation exposure.

Figure 3c shows the ICE image of a typical example of a patient with a PFO undergoing catheter ablation of the tunnel. In addition to undergoing a PVAI, this patient also had ablation performed of the tunnel surface of the SP along the zone of overlap.

At the end of the procedure, only one patient did not show a bubble shunt. However, at the 3-month follow-up, all patients except one showed an absence of any interatrial communication. The presence for a PFO was examined in all patients with a TTE accompanied by agitated saline injected during a Valsalva maneuver via an upper extremity intravenous cannula. Attention was paid in carefully examining ultrasound images of the septum as well as the atria especially both in strain phase and the release phase of the Valsalva maneuver. At the 3-month follow-up, no patient underwent transesophageal echocardiography (TEE). Patients in the ablation group were all enrolled in a prospective registry and followed. Three had a late recurrence of AF at a mean follow-up of 4.2 ± 1.4 years but there were no early or late procedure-related complications.

An ICE image of a patient with a PFO who underwent a prior PVAI as well as a PFO ablation is seen in Fig. 3d. The image was recorded after injection of agitated saline and during a Valsalva maneuver. Possibly due to fusion between the SP (white arrow) and SS (black arrow), there is no flow of agitated saline into the LA. This patient previously had a PFO with demonstrable right to left shunting.

4 Discussion

Several years ago, we described an anatomical entity termed LASP [14]. The structure provides insights about how adhesions form between the adjacent surfaces of the SP and SS and thus result in the closure of a FO. Based on this, we hypothesized that it may be feasible to artificially stimulate its delayed closure by injury (induced by mechanical trauma or by application of RF energy) to the tunnel surfaces of the SP and SS. Even though we are presenting a combination of a retrospective analysis of the mechanical injury subgroup and a prospective analysis of the RF injury, there is a common theme here. Injuring the FO through different mechanisms gives rise to the same end result, i.e., PFO closure.

Reason for accessing the LA via a PFO In the early days of ablation, accessing the LA via a PFO was not uncommon. Electrophysiologists who have performed ablations for a few decades were part of the early experience in which a PFO was used. However, the technique is now considered unfavorable, especially for AF ablations. The reason we examined ablation procedures between 2000 and 2006 was that since then, there was a shift in the corresponding author's technique to access the LA. Even when a PFO was present, it was considered preferable to puncture the low FO.

Closure of asymptomatic PFOs We did not intend to test whether there is value in closing asymptomatic PFOs. Instead, it was to test a "proof of concept" of closing PFOs in patients who were getting an AF ablation and was done as part of an investigational protocol. The ultimate aim is to use this technique and technology in patients with a valid indication, i.e., patients with PFOs and cryptogenic stroke.

Our imaging modality of choice was ICE to visualize the PFO and to help guide ablation catheter placement within the tunnel. We do not believe that closing PFOs with RF injury resulted in increased radiation exposure. Ablation within the tunnel is unlikely to result in damaging any adjacent structures such as the esophagus, phrenic nerve, bronchi, or the His bundle. All patients were anticoagulated for the first 3 months after the ablation and therefore, we feel that delivering RF energy within a PFO is unlikely to promote a higher risk of a thromboembolic event. Especially with PFO closure devices, there is a potential for long-term complications such as device erosion and migration. Patients in the ablation group were all enrolled in a prospective registry and followed. While three patients had a late recurrence of AF at a mean follow-up of 4.2 ± 1.4 years, there were no early or late procedure-related complications.

Role of PFO in cryptogenic strokes The PFO has been long suspected of playing an important role in the genesis of cryptogenic stroke. The evidence recently got markedly stronger. It

is also the most common cardiac finding in young patients (< 55 years of age) with an unexplained cerebrovascular event, presumably caused by paradoxical emboli. The presumed mechanism is the migration of a thrombus from the venous system to the LA via a PFO, with subsequent systemic embolization. Randomized trials in patients who have a PFO and an embolic event, comparing closure with anticoagulation or antiplatelet therapy, have firmly implicated the PFO in strokes due to a paradoxical embolism. Over the past few years, the anatomical entity has received a markedly increased attention.

Link between observation of LASP, patterns of fusion of PFO, and the current study The discovery of the LASP provided us unique insights into how the FO closes, i.e., the formation of adhesions between the SP and SS along the zone of overlap. Based on these insights, we hypothesized that (a) to close the PFO, one does not have to create a fusion along the entire zone of overlap and (b) the ideal way to close a PFO is to simulate/recreate the natural history of PFO closure, i.e., to promote adhesions between the tunnel surfaces of the SP and SS. In Fig. 4, we provide a pictorial sequence of events that likely occur upon injury created along the tunnel surfaces of the PFO with an eventual fusion of the FO.

Is it possible that we are creating a LASP and, by doing so, are creating a potentially problematic structure? It is true that the discovery of the LASP was the initial catalyst of the current project and our intention was to achieve closure of the PFO without device implantation [14]. However, our purpose was not to intentionally create a LASP. RF ablation was delivered along the entire tunnel surface of the SP (and unintentionally, probably the adjacent SS as well) and not just the caudal portion of the zone of overlap. Furthermore, a LASP is thrombogenic only under very special circumstances, i.e., when blood flow from the right pulmonary veins is compromised such as with mitral stenosis or with high filling pressures seen with congestive heart failure.

Importance of disrupting endothelial integrity Our results suggest that injury or endothelial denudation of the tunnel surfaces of the SP and SS results in the development of adhesions between the structures. With currently available technology, injury with RF energy is the most effective method of achieving endothelial denudation [15]. Based on its effects on endothelium, cryothermal energy is unlikely to have a similar effect. Two phenomena need to occur from the ablation to achieve fusion of the PFO: (a) endothelial denudation of the tunnel surfaces of the FO and (b) swelling of the SP and SS. While mechanical injury may cause endothelial denudation with reasonable efficacy, we feel that RF ablation is more likely to cause tissue swelling and edema. This may explain why compared to mechanical trauma, RF ablation using the settings described are much more potent in achieving PFO closure. The ideal power setting and RF duration to achieve this are unclear at this time. We expect that future studies will provide the answers.

We hypothesize that the healing process will result in adhesions developing between the SP and SS resulting in a subsequent closure of the PFO. Our method assumes that demonstrating acute closure is not important and does not reflect the likelihood of long-term success. In panels A–D of Fig. 4, we provide an illustrative display of what we feel occurs with induced injury along the tunnel surfaces of the SP and SS. We hope that our data will trigger a larger prospective trial to test this hypothesis.

PFO closure without a permanently implanted device Transcatheter closure of PFOs without the use of implantable devices can generally be divided into two approaches:

(i) Injury and endothelial denudation of adjacent tissues with delayed fusion and fibrosis are thought to occur when the adjoining tunnel surfaces of the SP and SS are injured using mechanical measures such as abrasion or thermal injury with RF ablation. We hypothesize that the healing process will result in adhesions between the septal components, resulting in its fusion. In this scenario, demonstrating acute closure is not important and does not predict long-term success. This is the concept that was tested in the current study and we believe that this is how a PFO closes naturally. The distinguishing feature is that when energy application takes place, it is within the PFO tunnel.

(ii) The concept of tissue fusion or welding emphasizes bringing tissues together (using vacuum suction or with other methods) and then applying radiofrequency energy [12, 13]. The *acuity of the closure* distinguishes this from the other concept described above. In the paradigm 1 clinical study, Sievert et al. demonstrated that transcatheter closure of a PFO without a permanent implant is technically feasible. The PFX-15 catheter system consists of a vacuum suction system to achieve an approximation of the SP and SS. It then affects closure of the PFO by welding the septal tissues together with RF energy application. The entire procedure is performed from the *right atrial side* of the septum, with *no energy application being performed within the PFO tunnel.* Thirteen (43%) of the 30 patients experienced PFO closure after the first procedure. Nine patients whose PFOs remained patent after the first procedure were elected to receive a second procedure using RF energy. The PFO was closed for 6 of those patients after the second procedure, resulting in a secondary closure rate of 63%. We believe that the

main reason for the low success rate after the initial procedure is because RF energy application is applied only to the right atrial surface of the SP and SS rather than within the tunnel surfaces of the two structures.

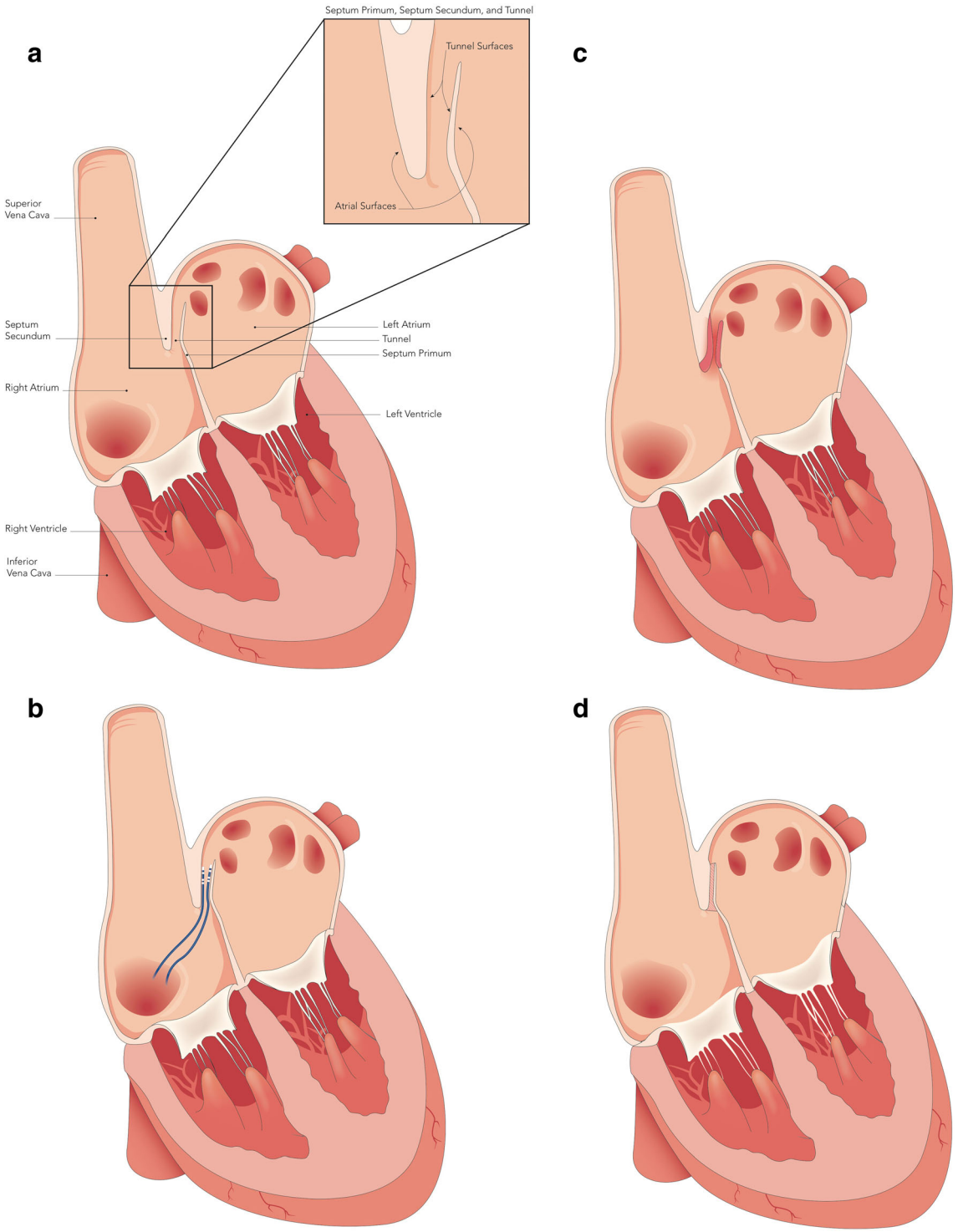

Fig. 4 **a** Cartoon depicting the different components of the interatrial septum in a heart with a patent foramen ovale. The septum primum and secundum are felt to have two surfaces—an atrial surface and a tunnel surface. **b** Illustration of application of RF energy along the opposing (tunnel) surfaces of the septum primum and secundum in the zone of overlap. **c** Reddish brown discoloration along the tunnel surfaces of the foramen ovale illustrates creation of injury, inflammation, and endothelial denudation along the opposing/tunnel surfaces of the septum primum and secundum in the zone of overlap. **d** Secondary to changes seen in **c**, development of adhesions occur between the septum primum and secundum along the zone of overlap, resulting in a closure of the foramen ovale

Similar to device closure of the LA appendage, procedures attempting PFO closure are likely to add to the growing interface between interventional cardiology and electrophysiology.

5 Limitations

(i) Our study, while provocative and novel, is small with a limited number of patients. It is not unusual for other novel pilot studies to have similarly small sample sizes. Given the promise that this intervention holds, it is our every intention to follow this up with studies in larger patient populations.

(ii) In diagnosing a PFO, TEE may be superior to TTE and, when combined with a Valsalva maneuver and agitated saline injection, is considered to be the imaging procedure of choice in patients with paradoxical embolism [16–19]. In the RF subgroup at follow-up, a PFO was tested with a TTE and agitated saline injection during a Valsalva maneuver, via an upper extremity intravenous line. Because of the orientation of the inferior vena cava to the FO, a PFO may theoretically be missed if the saline is administered through a cubital vein, as these bubbles may be redirected from the FO across the tricuspid valve into the right ventricle [20]. TTEs however do have a role in diagnosing PFOs and represent what is most commonly used in the "real world." When combined with harmonic imaging, the sensitivity and specificity of TTEs can be comparable to TEEs [19, 21]. TTEs do not require sedation and thus allow for a vigorous Valsalva maneuver—something that cannot be done with TEEs [19, 21].

6 Conclusion

The PFO closure technique demonstrated in our manuscript shows a promise and is low risk. We hope that it will stimulate larger prospective studies.

Compliance with ethical standards

Conflict of interest Andrea Natale: Speaker's Bureau: Boston Scientific, Biosense Webster, and St. Jude Medical. Consultant/Advisory Board: Biosense Webster, Boston Scientific, Medtronic, and St. Jude Medical.

Luigi Di Biase: Consultant for St. Jude Medical, Biosense Webster, Stereotaxis, and Boston Scientific. Recipient of travel and speaker's honoraria from Bristol Myers Squibb and Biotronik.

Subramaniam C. Krishnan: In 2006, Dr. Krishnan had applied for a patent on PFO closure technology that has since been abandoned.

References

1. Hagen PT, Scholz DG, Edwards WP. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984;59:17–20.
2. Holmes DR Jr, Cohen H, Katz WE, Reeder GS. Patent foramen ovale, systemic embolization and closure. Curr Prob Cardiol. 2004;29:56–94.
3. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med. 1988;318:1148–52.
4. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med. 2017;337:1030–2.
5. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377:1011–21.
6. Søndergaard L, Kasner S, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017;377:1033–42.
7. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med. 2003;139:753–60.
8. Onorato E, Melzi G, Casilli F, Pedon L, Rigatelli G, Carozza A, et al. Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. J Interv Cardiol. 2003;16:43–50.
9. Billinger K, Ostermayer SH, Carminati M, de Giovanni J, Ewert P, Hess J, et al. HELEX septal occluder for transcatheter closure of patent foramen ovale: multicenter experience. Eutointervention. 2006;1:465–71.
10. Braun MU, Fassbender D, Schoen SP, Haass M, Schraeder R, Scholtz W, et al. Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. J Am Coll Cardiol. 2002;39:2019–25.
11. Krumsdorf U, Ostermayer S, Billinger K, Trepels T, Zadan E, Horvath K, et al. Incidence and clinical course of thrombus formation on atrial septal defect and patient foramen ovale closure devices in 1,000 consecutive patients. J Am Coll Cardiol. 2004;43:302–9.
12. Hara H, Jones TK, Ladich ER, Virmani R, Auth DC, Eichinger JE, et al. Patent foramen ovale closure by radiofrequency thermal coaptation. First experience in the porcine model and healing mechanisms over time. Circulation. 2007;116:648–65.
13. Sievert H, Fischer E, Heinisch C, Majunke N, Roemer A, Wunderlich N. Transcatheter closure of patent foramen ovale without an implant. Initial clinical experience. Circulation. 2007;116:1701–6.
14. Krishnan SC, Salazar M. Septal pouch in the left atrium: a new anatomical entity with potential for embolic complications. JACC Cardiovasc Interv. 2010;3:98–104.
15. Khairy P, Chauvet P, Lehmann J, Lambert J, Macle L, Tanguay JF, et al. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation. 2003;107:2045–50.
16. Pearson AC, Labovitz AJ, Tatineni S, Gomez CR. Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. J Am Coll Cardiol. 1991;17:66–72.

17. Lee RJ, Bartzokis T, Yeoh TK, Grogin HR, Choi D, Schnittger I. Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke. 1991;22:734–9.
18. Chenzbraun A, Pinto FJ, Schnittger I. Biplane transesophageal echocardiography in the diagnosis of patent foramen ovale. J Am Soc Echocardiogr. 1993;6:417–21.
19. Pinto FJ. When and how to diagnose patent foramen ovale. Heart. 2005;91:438–40.
20. Gin KG, Huckell VF, Pollick C. Femoral vein delivery of contrast medium enhances transthoracic echocardiographic detection of patent foramen ovale. J Am Coll Cardiol. 1993;22:1994–2000.
21. Clarke NRA, Timperley J, Kelion AD, Banning AP. Transthoracic echocardiography using second harmonic imaging with Valsalva manoueuvre for the detection of right to left shunts. Eur J Echocardiogr. 2004;5:176–81.