TOPICS IN REVIEW

Lessons learned from experimental models of cerebrovascular aneurysms to improve endocardial device occlusion of the left atrial appendage

Subramaniam C. Krishnan, MD, FHRS,* Andrea Natale, MD, FHRS†

*From the *Sutter Heart and Vascular Institute, Sacramento, California, and †The Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, Texas.*

In patients with atrial fibrillation, left atrial appendage (LAA) occlusion devices represent an alternative to anticoagulation but are associated with residual peridevice leaks (PDLs) and device-related thrombi (DRT). Similarly, cerebrovascular aneurysms can be treated with coil embolization, but pericoil leaks represent a significant limitation. In experimental models of cerebrovascular aneurysms, endothelial denudation achieved independently with (1) embolization with radioactive coils, (2) mechanical removal of the endothelium, or (3) radiofrequency ablation was dramatically effective in preventing or eliminating pericoil leaks.

Anatomical, physiological, and blood flow similarities exist between the LAA and saccular aneurysms. Concepts developed in treating aneurysm leaks can be used to treat similar problems in the LAA. Learning from aneurysms, we conceived of a novel technique to denude local endothelium and thus eliminate residual leaks around LAA-occlusion devices. We recently successfully tested this hypothesis in patients with a PDL in a prospective manner in a multicenter study. In this article, we expand on the rationale of the technique developed to close PDLs and potentially also prevent DRTs.

KEYWORDS Endothelial; Denudation; Leaks; Watchman devices; Thromboembolism; Appendage

(Heart Rhythm O2 2021;2:423–430)

Introduction

In atrial fibrillation (AF) patients with strokes, thromboemboli originate from the left atrial appendage (LAA) in the vast majority.[1] The mainstay therapy of anticoagulation has multiple associated problems, prompting a search for alternative approaches, including mechanically excluding the LAA from the systemic circulation.[2,3].

Implantation of LAA-occluding devices such as the Watchman device (WMD) represents an alternative to anticoagulation but often has residual peridevice leaks (PDLs) and a significant incidence of device-related thrombi (DRT).[4–7] Similarly, cerebrovascular aneurysms can be treated with coil embolization (CE), but pericoil leaks represent a significant limitation.[8] In experimental models of cerebrovascular aneurysms, endothelial denudation (ED) achieved independently with (1) embolization with radioactive coils, (2) mechanical removal, or (3) radiofrequency ablation (RFA) was exceedingly effective in preventing or eliminating gaps between the coils and the aneurysm wall; it also effectively enhances neointimal covering over the coil.[9–13]

There are some anatomical, physiological, and blood flow similarities between the LAA and experimental models of saccular aneurysms, including the presence of an endothelial layer. We hypothesized that concepts developed in treating and preventing leaks in experimental aneurysm models, especially the dramatic effects of ED, can be used to treat similar problems in the LAA. We have previously demonstrated that in patients with a patent foramen ovale (PFO), ED achieved by mechanical abrasion or RFA can induce a subsequent spontaneous closure of the PFO.[14] We were therefore aware of the potential of ED to creation adhesions between neighboring tissues.

By understanding lessons learned from aneurysm models, especially the importance of local ED, we developed a procedure using RFA to denude the local endothelium of the appendage neck and thus solve the problem of residual leaks around LAA occluding devices (illustrated in Figure 1). Although difficult to verify, based on the experience with experimental aneurysm models, we also feel that in this process, the likelihood of covering the fabric of the WMD with a neointimal layer will be markedly enhanced, and thus this process may also lower the likelihood of DRT. We recently successfully tested this hypothesis in 43 patients with a PDL in a prospective manner in a multicenter study.[15]

In this article, we expand on the rationale of the technique developed to close PDLs and potentially also prevent DRTs. The evolution of our hypothesis and our initial success makes for an interesting and compelling story. If a therapeutic

Address reprint requests and correspondence: Subramaniam C. Krishnan, Arrhythmia Services, Sutter Medical Center, 2800 L St, Sacramento, CA 95816. E-mail address: Krishnan_sc@hotmail.com.

https://doi.org/10.1016/j.hroo.2021.06.004

KEY FINDINGS

- In atrial fibrillation patients, left atrial appendage (LAA) occlusion devices, an alternative to anticoagulation, are associated with peridevice leaks and device-related thrombi.
- Similarly, cerebrovascular aneurysms can be treated with coil embolization, but pericoil leaks represent a limitation.
- In experimental models of aneurysms, endothelial denudation by embolization with radioactive coils, mechanical debridement, or radiofrequency ablation was dramatically effective in preventing or eliminating leaks.
- Anatomical, physiological, and blood flow similarities exist between the LAA and aneurysms.
- Concepts developed in treating aneurysm leaks can be used to treat similar problems in the LAA.
- We conceived of a technique to achieve local endothelial denudation and eliminate leaks around appendage-occlusion devices and successfully tested this concept in 43 patients.

procedure is effective, it is important to understand why, and this is our focus. We aim to provide the reader with a mechanistic approach, predicated on the hypothesis that a greater insight into the underlying mechanisms will lead to a more successful and rationally chosen therapy that will be safer, enduring, and more effective.

Data from clinical study

Della Rocca and colleagues[15] recently completed a prospective multicenter study on RFA to treat PDLs that occurred after LAA occlusion in 43 patients (mean age: 75 ± 7 years; CHA_2DS_2-VASc: 4.6 ± 1.4) with acute (19) or chronic (24) evidence of moderate or severe PDL (gap dimension >4 mm) with 2 generations of WMDs (Watchman 2.5 and Watchman FLX).

The majority of patients underwent a repeat left atrial ablation procedure with an open irrigated catheter with contact force sensing, targeting the appendage ostium (median of 18 radiofrequency [RF] applications per patient; mean maximum contact force of 16 g; mean power of 44 watts; mean RF time of 5.1 minutes). All were maintained on a direct oral anticoagulant post procedure. The investigators were able to obtain 100% acute success rate and 88% chronic success rate at a median follow-up of 48 days with repeat transesophageal echocardiography (TEE) imaging. Follow-up TEE revealed complete LAA sealing in 23 (53.5%) cases and a negligible residual leak in 15 (34.9%). One patient had a steam pop with a pericardial effusion requiring pericardiocentesis. No thromboembolic events or device dislodgements were seen at a follow-up of 7 months. In 12 patients, episodes of abrupt impedance decrease happened when the catheter tip came into contact with the nitinol frame of the WMD. Panels A–D of Figure 1 with TEE images on the left and cartoon drawings on the right illustrate and summarize the salient features of the procedure.

The investigators concluded the following: (1) Catheter manipulation and RF energy applications in proximity to WMDs are likely safe, with no device dislodgements. (2) RF energy application at the atrial edge of a PDL was successful in achieving leak closure in a high percentage of patients. Even though our hypothesis initially called for the ablation being performed differently (ie, within the appendage side of the leak, as shown in the right half of Figure 1B), the occurrence of a steam pop and pericardial effusion necessitated a change in strategy (ie, ablation at the atrial edge rather than immediately inside the appendage).

The problem of peridevice leaks and how the solution evolved

Endocardial device occlusion of LAA

AF patients account for a sixth of all strokes, and thromboemboli originate from the LAA in the vast majority.[1] The mainstay therapy of anticoagulation has multiple associated problems.[2] These drawbacks have prompted a search for alternative approaches, including mechanically excluding the LAA from the systemic circulation. Removing the LAA at the time of cardiac surgery represents an attractive alternative strategy and includes ligation, clipping, and amputation. Appendage removal is recommended in patients with valvular disease undergoing cardiac surgery.[3]

Devices have been developed that can plug the LAA endocardially. Prominent is the WMD (Boston Scientific, Natick, MA), whose atrial side is covered with a polyester membrane that filters thrombi formed in the LAA. Randomized trials in patients with AF show that occlusion with the WMD is noninferior to anticoagulation.[4] Based in part on the trials, the US Food and Drug Administration approved the use of the WMD for use in patients with AF. Since then, it has been used increasingly.

Limitations of LAA occlusion devices

Peridevice leaks

WMD implantation and management of patients with LAA devices can be complex and problematic, with PDLs occurring in a third of cases.[5] These gaps can persist and enlarge over time, while new gaps can also develop.[16] Incomplete surgical LAA exclusions lead to a persistent communication between the LAA and the systemic circulation.[17,18] Consequently, a thrombus forming inside the LAA can still embolize. The correlation between peri-WMD leaks and risk of thromboembolism remains poorly understood. Literature examining surgically excluded LAA and the LARIAT device shows that incomplete closure is associated with increased incidence of subsequent thromboembolism, regardless of

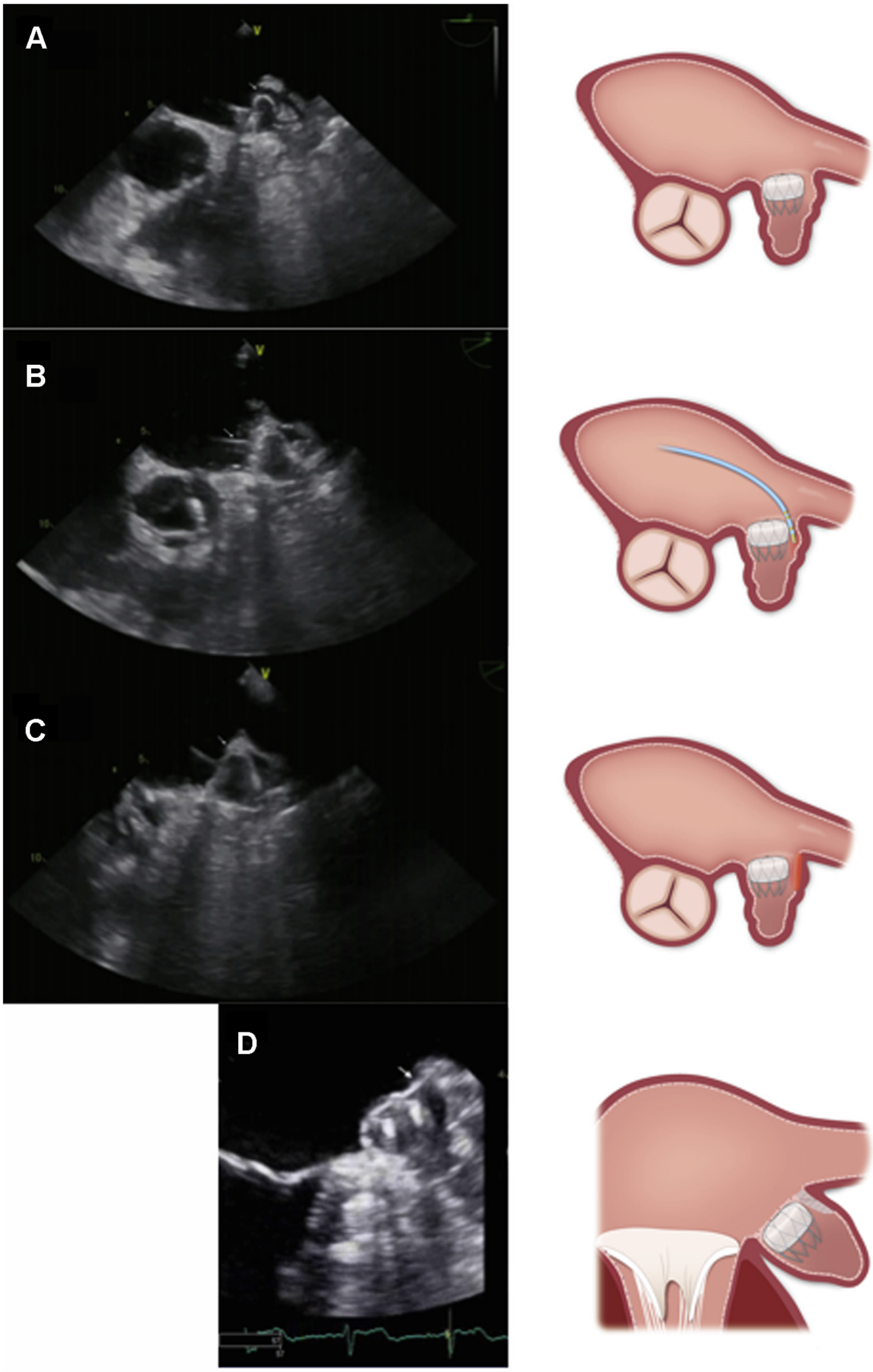

Figure 1 A 71-year-old patient with atrial fibrillation who underwent a simultaneous ablation and a 27 mm Watchman device implantation with a large acute leak. **A:** Transesophageal echocardiography (TEE) image (left) and corresponding cartoon image depicting the leak (right). **B:** Left image shows ablation catheter (*white arrow*) placed within the leak. During radiofrequency ablation, bubbles are seen. **C:** Left image shows inflammation and edema at the ablation site (*white arrow*), appearing thicker and more echogenic. **D:** Left image shows a TEE image obtained 3 months later, showing complete occlusion with adhesions at the appendage ostium. The corresponding cartoon image (right) depicts expected fibrosis and leak closure.

the size of the residual leak.[16,18] It is still debated whether a causal relationship exists between thromboembolism and peri-WMD leaks. It is accepted practice to continue anticoagulation in patients with leaks greater than 5 mm. This 5-mm threshold is completely arbitrary; the literature inconsistently correlated larger leaks with a higher incidence of strokes. Suboptimal WMD seating can also cause dislodgement and embolization, sometimes with fatal consequences.[19]

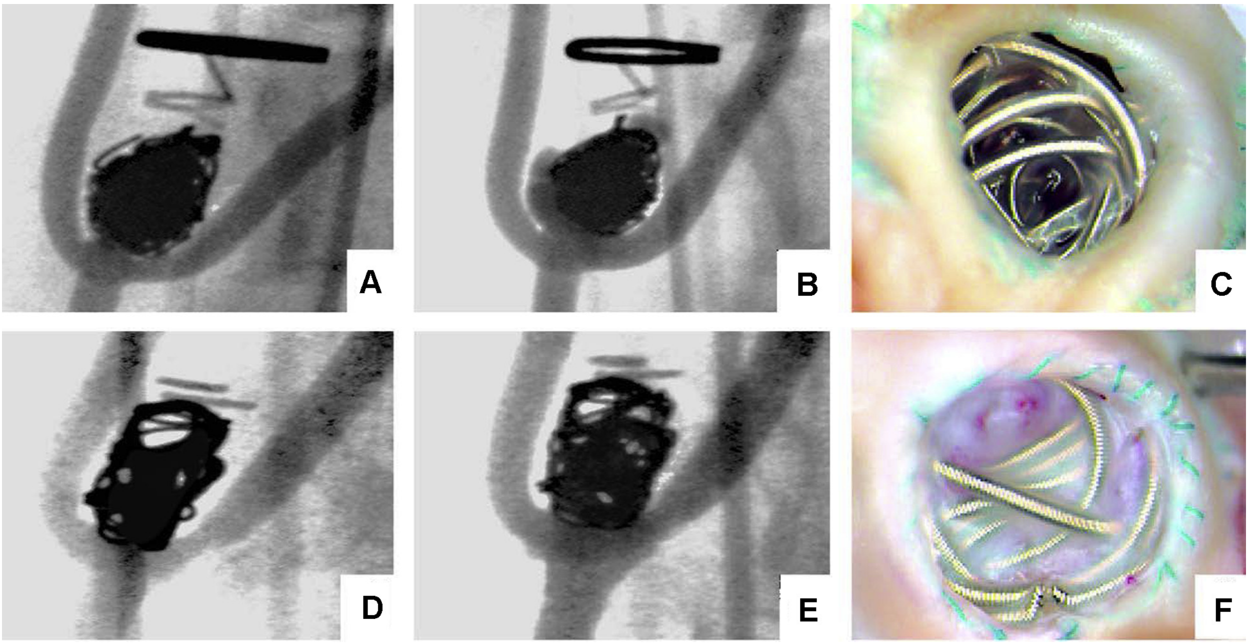

Figure 2 Angiographic and macroscopic results after mechanical endothelial denudation (ED) and coiling of canine bifurcation venous pouch aneurysm. Selected views of angiograms performed immediately (**a, d**) and 3 months (**b, e**) after coiling, preceded (**d, e**) or not (**a, b**) by endothelial denudation. Large recurrence 3 months after coiling is seen (**b**), whereas aneurysms treated with denudation remain occluded (**e**). En face macroscopic view of the aneurysm shows that neointima formation at the neck at 3 months is more complete after ED (**f**) as compared with controls (**c**). (Image borrowed with permission from Raymond J, Guilbert F, Metcalfe A, Gevry G, Salazkin I, Robledo O. Role of the endothelial lining in recurrences after coil embolization. Prevention of recanalization by endothelial denudation. Stroke 2004;35:1471-1475.)

Device-related thrombi

In patients with LAA occlusion devices, complete endothelialization of the device may not occur with an increased risk of PDL and DRT. There is wide variation in the reported incidence of DRT owing to differences in the type of LAA occlusion device, choice and duration of postprocedural antithrombotic regimen, and timing of surveillance imaging, ranging from 3.7% to 7%. When present, it is associated with a higher incidence of stroke and systemic embolism.[6,7]

Predictors of DRT following LAA closure include a history of transient ischemic attack or stroke, permanent AF, vascular disease, larger LAA diameter, and a lower left ventricular ejection fraction. The underlying mechanism is thought to be incomplete device endothelialization and exposed metal at the attachment site of the retaining wire with the screw.

Until additional data are obtained, optimal sealing of the LAA should be a priority as implantation techniques improve. An incomplete occlusion is worse than no occlusion, and there is a compelling necessity to eliminate leaks.

Improving seating of LAA devices: Lessons from endovascular coiling of intracranial aneurysm models

CE with the Guglielmi detachable coils has revolutionized the treatment of intracranial aneurysms and has been shown to be superior to surgical clipping.[8] However, a significant proportion of patients with these coils have incomplete residual filling and gaps, with continuing concerns for future hemorrhages. Significant efforts have been undertaken to understand and eliminate these leaks. The healing mechanisms after coiling and the reasons for the recurrent leaks were poorly understood. This created a necessity for experimental animal models to allow for a deeper understanding of the mechanisms involved in the progression and rupture of aneurysms and to also facilitate testing of devices.

Initially, researchers proposed a concept of "*deficient healing*," deficient endothelialization, and neointima formation. In fact, they actually attempted to stimulate endothelialization and fibrosis through different mechanisms, including coating the coils with vascular endothelial growth factor, collagen, and fibroblast growth factors.[20] These studies showed mostly modest effects.

Studies conducted at the University of Montreal showed the opposite—ie, that the endothelial lining is the key factor responsible for residual leaks. Their findings created a paradigm shift in our understanding of this process.

Their research progressed in 4 stages:

(1) Animal model creation: They first developed a carotid bifurcation venous pouch aneurysm (VPA) model resembling a saccular aneurysm, that has a well-defined neck, does not thrombose spontaneously, and can be coiled completely.[9] Residual leaks are frequent.
(2) Embolization with radioactive coils: Early on, they investigated coils emitting low-grade radiation in canine

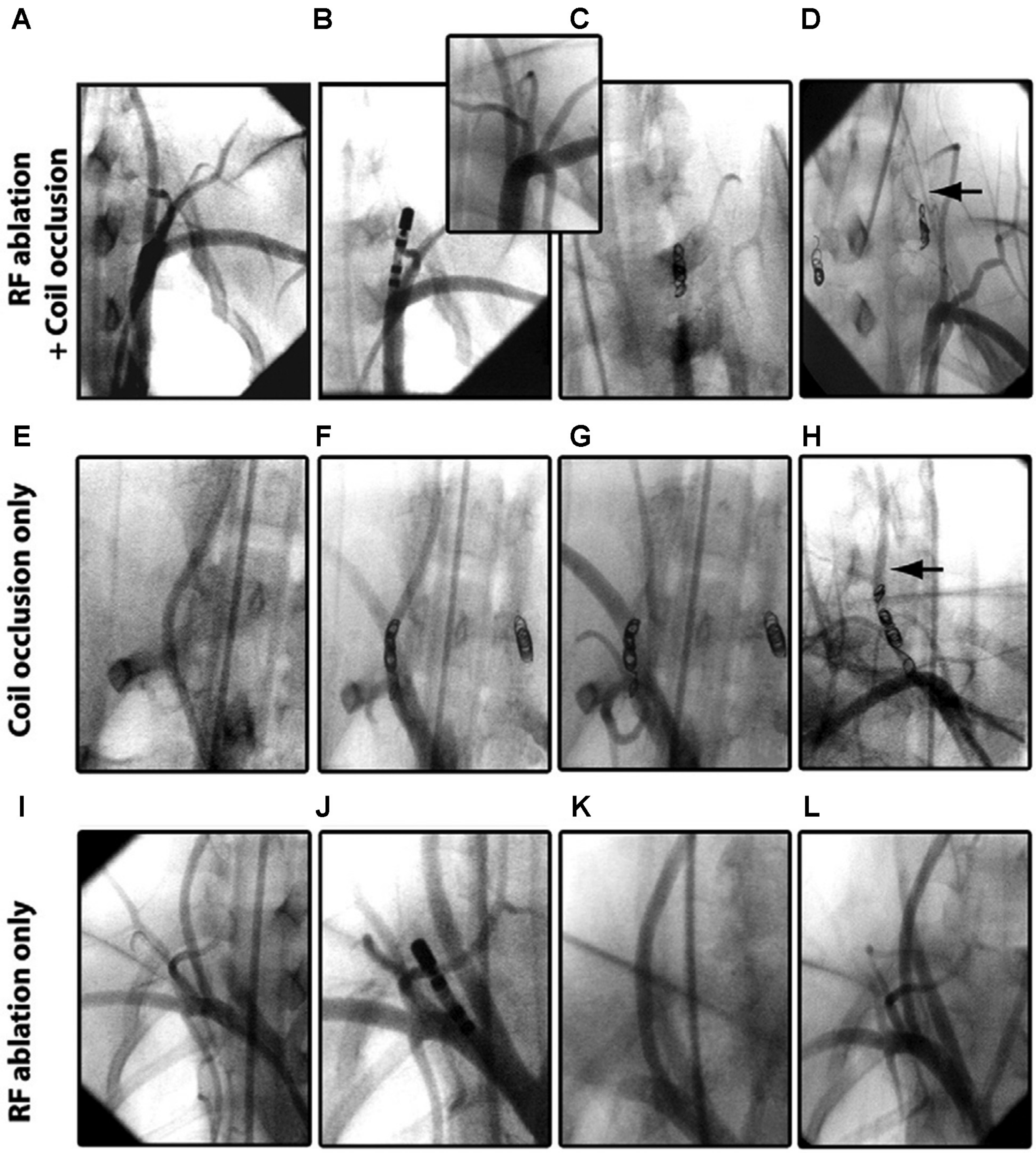

Figure 3 Prevention of canine vertebral artery recanalization after coil occlusion by radiofrequency (RF) ablation: angiographic results. Subclavian angiograms obtained before (**a,e,i**), immediately after (**f**), and at the end of the procedure (**c,g**), and 1 month after (**d,h**) coil occlusion of vertebral artery show recanalization of the right vertebral artery (*arrow* in **h**) but no recanalization (*arrow* in **d**) when RF ablation is applied before coil embolization (**b**). RF ablation alone (before coil occlusion in insert in **b** and without coil occlusion in **j,k,l**) does not lead to substantial angiographic changes. In this model, coil occlusion without ablation of the endothelial lining (**e–h**) routinely leads to occlusion by 1 hour (**g**) that recanalized at 2 weeks (**h**). (Image borrowed with permission from Raymond J, Savard P, Salazkin I, Bouzeghrane F. Radiofrequency endothelial ablation prevents recanalization after endovascular coil occlusion: in vitro and in vivo assessment. J Vasc Interv Radiol 2010;21:101–107.)

maxillary arteries and VPA models[10] and compared it to conventional coils. The radioactive coil group showed persistent complete occlusion while the conventional coil group showed full recanalization with endothelium-lined gaps. They concluded that radiation destroys the local adjacent endothelium within the aneurysm adjacent to the coils and thus prevents recanalization and residual leaks. When present, endothelium prevents thrombosis at the interface between the coil and the aneurysm wall.

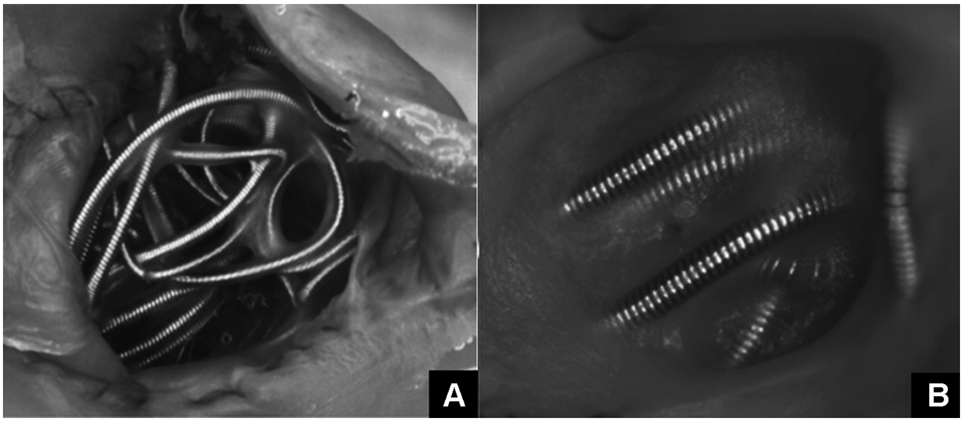

Figure 4 Results of bipolar radiofrequency (RF) ablation performed between an endovascular stent and the coil of coiled bifurcation venous pouch aneurysms 3 months after procedure. **A:** En face view of control pouch with coiling alone. **B:** Aneurysm treated with endovascular coiling and bipolar radiofrequency ablation. Neointimal closure of the aneurysm neck was dramatically better with RF ablation compared with controls. There is now no gap between the coil and the aneurysm wall, with complete sealing of the aneurysm neck. In addition, there is a layer of neointimal tissues covering the coil. (Image borrowed with permission from Boileau X, Zeng H, Fahed R, et al. Bipolar radiofrequency ablation of aneurysm remnants after coil embolization can improve endovascular treatment of experimental bifurcation aneurysms. J Neurosurg 2017;126:1537–1544.)

(3) Mechanical removal of endothelium: The same investigators further developed their hypothesis by intentionally removing the endothelium with mechanical debridement or by inverting the venous pouch during aneurysm construction.[11] Strikingly similar to the results with radioactive CE, after local ED, recanalization failed to occur (Figure 2).

(4) Endothelial destruction achieved by RFA: RFA has been developed for decades for treatment of arrhythmias and for venous diseases of the lower extremities. It is the most practical method to achieve ED of the ablated tissues. The Montreal group studied the effect of CE combined with RFA on canine vertebral arteries.[12] Similar to radioactive CE and with mechanical ED, no recanalization after CE was seen if RFA was performed before coil deposition. The dramatic effects of RFA on achieving persistent occlusion after CE are shown in Figure 3. In addition, bipolar ablation using the coil and an endovascular stent as electrodes selectively eliminated leaks in VPAs after CE (Figure 4).[13] Figures 2 and 4 also show that ED of the aneurysm neck is now also followed by a complete covering of the coil with a neointimal layer.

ED and PFO closure

We recently published that ED achieved mechanically or with ablation can trigger fusion between the tunnel surfaces of the septum primum and secundum in the heart and thus achieve closure of a PFO.[14] Our investigations on PFOs was how we first became familiar with the ability of ED to create adhesions between adjacent tissues. However, it was only after we reviewed the findings on the VPA model that we gained confidence that our hypothesis will work.

Similarities and key differences between an aneurysm and the LAA

Unlike the right atrial appendage, which is a pyramidal structure with a wide ostium, the LAA has a well-defined neck and a narrow ostium. Like an aneurysm, the LAA is more compliant and distensible than the main body of the left atrium[21] and has blood flow similarities as well. The key similarity is the presence of an endothelial lining in both the LAA and experimental aneurysm models, thus allowing for ED. Based on the parallels between the experimental aneurysm model and the LAA, we hypothesized with confidence that ED will help eliminate PDLs in the LAA as well. The analogy to CE of saccular aneurysms can be faulted. The Guglielmi detachable coils are implanted in the arterial circulation rather than within the heart. The goal of CE is to prevent bleeding, while the goal of WMD implantation is to prevent thromboembolic strokes. The device itself is very different, as is the pressure and the surrounding tissue, especially the absence of adjacent brain tissue with the LAA. The potential for collateral damage, therefore, is dramatically different.[22]

In the VPA model, no matter how ED is achieved, it is highly effective in preventing or eliminating pericoil gaps, findings that are robust, reproducible, and difficult to ignore. It is based on these studies that we hypothesized with confidence that ED will be effective in eliminating PDLs in the LAA. The consistency and robustness of the data from the experimental aneurysm model gave us the confidence to apply the lessons learned to the LAA.

Potential antiarrhythmic benefits of LAA ablation

The LAA has been shown to be an important focus perpetuating AF. In patients with persistent longstanding AF, ablation and electrical isolation of the LAA may improve freedom from AF.[22] However, electrical isolation of the

LAA without endovascular device occlusion carries a risk of future thromboembolism.

LAA ablation and mechanical occlusion can be performed concomitantly.[23,24] This combination has the potential to improve ablation outcomes, lower stroke risk, and reduce bleeding risk by stopping long-term anticoagulation. In 2015, Panikker and colleagues[23] published their experience of LAA ablation to achieve electrical isolation of the structure with concomitant WMD implantation in 8 dogs. Autopsy examinations performed at 45 days showed complete device–tissue apposition and occlusion of the LAA, with mature connective tissue and endothelium enveloping the polyester fabric of the device in all animals. However, the central metal hub was completely covered in only 2 of the 8 animals. Interestingly, this project was conceived and implemented to achieve electrical isolation of the LAA with concomitant appendage occlusion. Achieving optimal seating of the WMD was not one of the aims of that project, but appears to be an unintended benefit.

Follow-up studies have satisfactorily addressed efficacy, safety, and feasibility of this technique in humans as well.[24] The device is likely to be seated better, with a substantially lower likelihood of future residual leaks. Of the 20 patients who underwent this combination procedure, only 1 had a persistent residual leak.[24]

Importance of understanding underlying mechanisms

It has been suggested that the underlying mechanism of RFA-induced PDL closure is contracture and collagen formation secondary to RFA.[15] While it is possible that these mechanisms could be relevant, there is very strong and compelling evidence that it is ED that is the key underlying mechanism. First, our PFO closure manuscript to which Della Rocca and colleagues refer also includes fusion/closure achieved with mechanical injury, presumably because of ED of the adjacent surfaces of the septum primum and secundum along the tunnel surfaces of the PFO. Similarly, in the VPA model studied by the Montreal group, ED—no matter how it is achieved (with local radiation, mechanical abrasion, pouch inversion, or RFA—is exceedingly effective in achieving closure of pericoil leaks.[9–13] It is therefore likely that achieving ED is the cornerstone of this procedure and not contracture or collagen synthesis. In 2017 when using RFA to achieve closure of LAA occlusion devices was initially proposed by us, ED was the primary intended focus.

Why is understanding the underlying mechanism important? The power settings, wattage, and contact force needed to achieve ED would likely be substantially different from what is needed to achieve tissue contracture; transmural necrosis may not be necessary. Therefore, the likelihood of steam pops, complications, and safety profiles will also be very different.

Della Rocca and colleagues[15] caution against the catheter tip wedging in the tunnel-like residual communication created by the LAA occlusion device (Figure 1B, right half of cartoon drawing). They feel that this may lead to sudden impedance rise with steam pops and was likely the mechanism that led to the complication observed. Based on this, they advise that the RF energy should be applied on the atrial edge of the leak at an ostial level. Is it really possible to be that precise? Will it lead to ED at the neck of the leak? Or are we in fact making a case to lower the power when delivering energy inside the tunnel? One can speculate that lower power is needed to achieve ED and is substantially less likely to cause steam pops.

One also realizes that ablation within the LAA before vs after WMD implantation are 2 very different procedures with dissimilar safety profiles. The risk of catheter wedging, sudden impedance rise, and steam pops are markedly lower when energy delivery is performed within an LAA that does not have a previously placed device. We call for a clinical trial where patients are randomized between a standalone implantation of the WMD and WMD that is preceded by RFA of the LAA ostium.

Will ED of the appendage improve neointimal covering of polyester fabric and of the exposed hub?

Fundamental to vascular healing, the neointima is a nonspecific vascular response to injury or foreign bodies, and is composed of mesenchymal cells and extracellular matrix covered by a single layer of endothelial cells.[25] Data from the experimental aneurysm models and the animal study by Panikker and colleagues[23] suggest that ED of the appendage neck will also result in a markedly enhanced covering of the polyester fabric/device surface with a layer of neointima and endothelium. Figures 2 and 4 show highly convincing supporting evidence. This raises the possibility that enhanced covering of the device with neointima will also cover the central hub. However, disappointingly, in the canine study by Panikker and colleagues,[23] the exposed metal was covered in only 2 out of the 8 animals. Whether, with ED, the smaller metal hubs in the newer versions of the WMD will be completely covered with neointima and endothelium remains to be seen. This is crucial, since the exposed metal hub is felt to be the key problem associated with DRT.[7]

Conclusion

Our main message is to draw attention to the potential for ED in preventing or eliminating PDLs around appendage occlusion devices. These effects were first noticed during studies of cerebrovascular aneurysm models where ED achieved independently by embolization with radioactive coils, mechanical removal, or RFA prevents or eliminates leaks around CE and also effectively creates a covering of a neointimal layer. Based on similarities between a saccular aneurysm and the LAA and between CE with detachable coils and LAA device occlusion, we hypothesized that lessons learned from the former can be applied to improve seating of the latter, to eliminate PDLs, and to also achieve neointimal covering of the device surface. The recently completed clinical study suggests that achieved ED of the appendage neck will have a definite role in improving device occlusion of the appendage.

Funding Sources

The study was supported in part with a grant from the Sutter Medical Center Sacramento foundation.

Disclosures

Andrea Natale: Speaker's Bureau: Boston Scientific, Biosense Webster, St. Jude Medical; Consultant/Advisory Board: Biosense Webster, Boston Scientific, Medtronic, St. Jude Medical. Subramaniam C. Krishnan owns intellectual property relating to (a) preventing strokes arising from the left atrial appendage and (b) treating hemorrhage arising from the left atrial appendage.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement

The clinical investigations discussed were approved by the institutional review board at St. David's Medical Center.

References

1. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–759.
2. Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–992.
3. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2008;118(15):e523–e661.
4. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 2011;123:417–424.
5. Viles-Gonzales JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman device in patients with atrial fibrillation. A PROTECT AF (Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation) substudy. J Am Coll Cardiol 2012;59:923–929.
6. Ellis CR, Piccini JP. Left atrial appendage closure two steps forward, one step back. Circulation 2018;138:886–888.
7. Dukkipati SR, Kar S, Holmes DR Jr, et al. Device-related thrombus after left atrial appendage closure: incidence, predictors, and outcomes. Circulation 2018; 138:874–885.
8. Molyneux AJ, Kerr RSC, Yu L, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366:809–817.
9. Raymond J, Darsaut T, Salazkin I, Gevry G, Bouzeghrane F. Mechanisms of occlusion and recanalization in canine carotid bifurcation aneurysms embolized with platinum coils: an alternative concept. Am J Neuroradiol 2008;29:745–752.
10. Raymond J, Leblanc P, Desfaits AC, et al. In situ beta radiation to prevent recanalization after coil embolization of cerebral aneurysms. Stroke 2002;33:421–427.
11. Raymond J, Guilbert F, Metcalfe A, Gevry G, Salazkin I, Robledo O. Role of the endothelial lining in recurrences after coil embolization. Prevention of recanalization by endothelial denudation. Stroke 2004;35:1471–1475.
12. Raymond J, Savard P, Salazkin I, Bouzeghrane F. Radiofrequency endothelial ablation prevents recanalization after endovascular coil occlusion: in vitro and in vivo assessment. J Vasc Interv Radiol 2010;21:101–107.
13. Boileau X, Zeng H, Fahed R, et al. Bipolar radiofrequency ablation of aneurysm remnants after coil embolization can improve endovascular treatment of experimental bifurcation aneurysms. J Neurosurg 2017;126:1537–1544.
14. Di Biase L, Burkhardt JD, Horton R, et al. Fusion of foramen ovale triggered by injury to tunnel surfaces of septum primum and secundum. J Interv Card Electrophysiol 2019;55:63–71.
15. Della Rocca D, Murtaza G, Di Biase L, et al. Radiofrequency energy applications targeting significant residual leaks after watchman implantation: a prospective, multicenter experience. JACC Clin Electrophysiol 2021 (in press).
16. Mohanty S, Gianni C, Trivedi C, et al. Risk of thromboembolic events after percutaneous left atrial appendage ligation in patients with atrial fibrillation: long-term results of a multicenter study. Heart Rhythm 2020;17:175–181.
17. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol 2008;52:924–929.
18. Aryana A, Singh SK, Singh SM, et al. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. Heart Rhythm 2015;12:1431–1437.
19. Aminian A, Lalmand J, Tzikas A, Budts W, Benit E, Kefer J. Embolization of left atrial appendage closure devices: a systematic review of cases reported with the Watchman device and the Amplatzer cardiac plug. catheterization and cardiovascular interventions 2015;86:128–135.
20. Abrahams JM, Forman MS, Grady MS, Diamont SL. Delivery of human vascular endothelial growth factor with platinum coils enhances wall thickening and coil impregnation in a rat aneurysm model. Am J Neuroradiol 2001;22:1410–1417.
21. Hoit BD, Shao Y, Tsai L, Patel R, Gabel M, Walsh R. Altered left atrial compliance after atrial appendectomy: influence on left atrial and ventricular filling. Circ Res 1993;72:167–175.
22. Di Biase L, Burkhardt JP, 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.
23. Panikker S, Virmani R, Sakakura K, et al. Left atrial appendage electrical isolation and concomitant device occlusion: a safety and feasibility study with histologic characterization. Heart Rhythm 2015;12:202–210.
24. Panikker S, Jarman JWE, Virmani R, et al. Left atrial appendage electrical isolation and concomitant device occlusion to treat persistent atrial fibrillation. a first-in-human safety, feasibility, and efficacy study. Circ Arrhythm Electrophysiol 2016;9:e003710.
25. Schwartz RS, Holmes DR Jr, Topol EJ. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. J Am Coll Cardiol 1992; 20:1284–1293.