TOPICS IN REVIEW

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

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In patients with atrial fibrillation, left atrial appendage (LAA) occlusion devices represent an alternative to anticoagulation but are associated with residual peri-device 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 (RFA) 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

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 peri-device 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 create 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

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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.

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. The mainstay therapy of anticoagulation has multiple associated problems. 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.

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. 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. These gaps can persist and enlarge over time, while new gaps can also develop. Incomplete surgical LAA exclusions lead to a persistent communication between the LAA and the systemic circulation. 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
the size of the residual leak.\textsuperscript{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.\textsuperscript{19}

\textbf{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. \textbf{A}: Transesophageal echocardiography (TEE) image (left) and corresponding cartoon image depicting the leak (right). \textbf{B}: Left image shows ablation catheter (white arrow) placed within the leak. During radiofrequency ablation, bubbles are seen. \textbf{C}: Left image shows inflammation and edema at the ablation site (white arrow), appearing thicker and more echogenic. \textbf{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.
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.22 Residual leaks are frequent.

2. Embolization with radioactive coils: Early on, they investigated coils emitting low-grade radiation in canine
maxillary arteries and VPA models\textsuperscript{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.
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. Strikingly similar to the results with radioactive CE, after local ED, recanalization failed to occur (Figure 2).

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. 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). 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 neo-intimal 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. 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 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 thrombo-embolic 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.

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. 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. 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 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. 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.

**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. 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,ouch inversion, or RFA—is exceedingly effective in achieving closure of pericocil leaks. 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 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 stand-alone 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.

Data from the experimental aneurysm models and the animal study by Panikker and colleagues 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, 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.

**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.

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**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.

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