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Vascular Healing After Arterial Access: A Histopathological Comparison of Standard Seldinger Versus a Novel Access Technology

BY RAHUL S. PATEL, MD; RENU VIRMANI, MD; FRANK D. KOLODGIE, PHD; DEBRA COGAN, RN; AND ZOLTAN TURI, MD

With the introduction of percutaneous arterial access by Seldinger in 1953, the need for surgical arteriotomy was eliminated.[1] However, potential trauma to the artery from needle puncture, the introduction of multiple catheters, and the process of closure was recognized early and has, to some degree, remained unresolved for 60 years. Manual compression is generally effective for closure, but it has a number of undesirable features, including discomfort, risks associated with stasis in the artery and adjacent vein during vessel occlusion, and the substantial inflammatory response associated with arteries subjected to manual compression.[2] A number of alternatives to manual compression have been introduced. Unfortunately, despite several generations of device development, the most recent studies of these devices still demonstrate that the optimal solution for arterial closure has not been achieved by the deposition of clips, plugs, or sutures into the arterial tract. Acute arterial complications, as well as the histopathological sequelae caused by closure device debris left behind in the arterial system and tissue tract, have been well documented.[3] In general, review of the literature and the FDA MAUDE (Manufacturer and User Facility Device Experience) database demonstrates that vascular closure device (VCD) use exposes patients to risks of bleeding, infection, and vessel obstruction among others.

The AXERA® 2 Access System (Arstasis, Fremont, CA) creates a shallow-angle arteriotomy of 10° to 15° compared to the standard 45° path typical of percutaneous arterial access

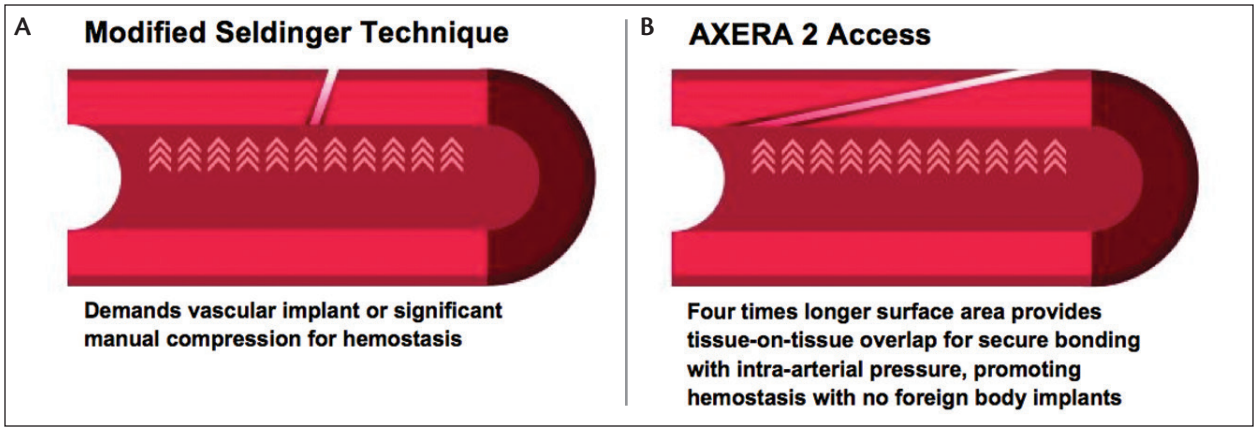

Figure 1. Depiction of the standard modified Seldinger technique arteriotomy with access through the arterial wall at a 45° angle (A) and the AXERA 2 access through the arterial wall at a shallow 10° to 15° angle (B).

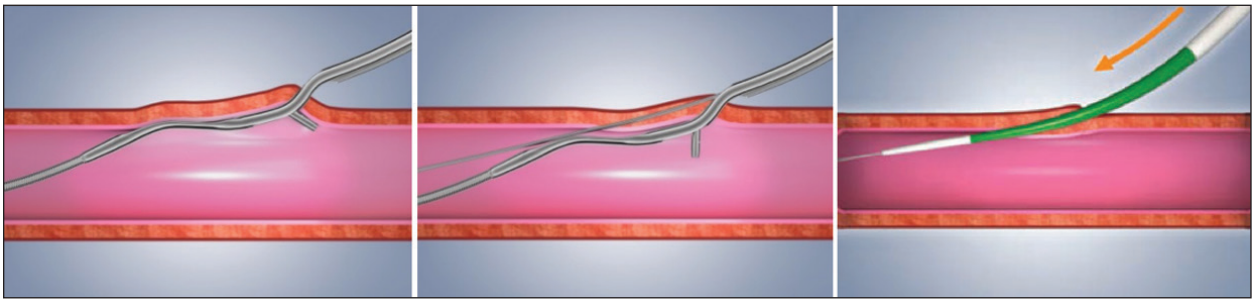

Figure 2. AXERA 2 procedural overview showing deployment of the heel for positioning of the micropuncture needle, which is deployed at a shallow 10° to 15° angle followed by sheath insertion over a guidewire using standard technique.

(Figure 1). This method is designed to maximize tissue-on-tissue overlap upon withdrawal of the femoral sheath, theoretically accelerating hemostasis by facilitating arterial sealing without an implant. This method has been shown to result in short compression times with safety and patient comfort superior to historical controls.[4,5] The histopathological effects on late-stage tissue healing with this novel shallow-angle access tract approach are unknown, and in general, despite the 60-year track record of percutaneous vascular access, few studies have examined vascular healing after the Seldinger approach in detail. Therefore, the aim of this study was to investigate vascular tissue responses and arterial healing of access sites after use of the modified Seldinger technique and the AXERA 2 Access System. Safety was assessed according to prespecified histopathological and procedure-related endpoints.

MATERIALS AND METHODS

Protocol

This study was designed for 30-day survival and included seven mature male Suffolk Crossbred sheep. The study was performed in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). The test facility is registered with the United States Department of Agriculture to conduct research in laboratory animals. Before initiation of the study, the study protocol and procedures were reviewed and approved by the Test Faculty's Animal Research Committee (ARC/Institutional Animal Care and Use Committee). The ovine model was chosen because it is similar to human anatomy,[6] its physiology is well-understood, and there is a range of published evidence that demonstrates acceptable translation of results from the ovine to human model.[7]

All animals were sedated, anesthetized, and prepped for a sterile procedure according to standard laboratory operating procedures. Carotid artery access facilitated angiography of both femoral arteries, establishing the baseline appearance of the vessels. In addition, ultrasound was performed to further establish the diameters of the femoral arteries. Additional angiograms were performed following vascular access prior to sheath insertion, following sheath insertion, and after manual compression.

Using ultrasound guidance, retrograde percutaneous vascular access was achieved in both the right and left superficial femoral arteries (SFAs) by a single operator experienced with the modified Seldinger technique and the AXERA 2 System. In all sheep, access to the right SFA was achieved with the AXERA 2 Access System, while the left SFA was accessed using the standard modified Seldinger (anterior wall puncture only) approach. Access was achieved in both right and left SFAs with a 19-gauge caliber needle.

The AXERA 2 access technique uses the deployment methodology shown in Figure 2. Briefly, after initial access to the artery and introduction of the device into the arterial lumen, the heel of the device is deployed, and the device is gently retracted, positioning a second needle of micropuncture caliber that creates a shallow-angle tract in which the procedure sheath is introduced for the subsequent catheterization procedure. Thus, at the AXERA site, there are two punctures of the arterial wall—the initial 19-gauge distal access site and the shallow-angle proximal micropuncture access site, through which the introducer sheath is inserted.

After 5-F sheaths were placed in both SFAs, the animals were anticoagulated with heparin (20–30 IU/kg) to achieve the target activated clotting time (ACT) of ≥ 180 seconds. ACT levels were measured to maintain this target. Each animal had 2 mg verapamil and 200 µg nitroglycerin administered into the right and left SFAs. Sheath removal occurred only after the ACT had normalized to baseline levels. After sheath removal, nonocclusive manual compression was held for 5 to 10 minutes until hemostasis had been achieved. Sheep were then allowed to recover and were maintained and observed daily for a subsequent 30 days without additional intervention.

Animals were euthanized 30 ± 2 days after the access procedures. A longer survival period was not required because there was no implant in the vasculature that could trigger the longitudinal development of foreign body granulomata or fibrotic encapsulation, which has been observed with vascular closure device implants.[8]

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TABLE 1. SEMI-QUANTITATIVE GRADING SYSTEM FOR FEMORAL ARTERY CLOSURE DEVICES

Parameter	0	1 (Trace)	2 (Mild)	3 (Moderate)	4 (Severe)
Endothelialization (% loss)	None	< 25%	25%–50%	51%–75%	> 75%
Fibrin/platelet thrombus	None	Focal	Multifocal	Regionally diffuse	Marked diffuse or total luminal occlusion
Inflammation	None	≤ 20 inflammatory cells per 40x HPF	21–100 inflammatory cells per 40x HPF	101–150 inflammatory cells per 40x HPF	≥ 150 inflammatory cells per 40x HPF
Giant cell reaction	None	2–5 GC per 40x HPF	6–10 GC per 40x HPF	11–25 GC per 40x HPF	≥ 26 GC per 40x HPF
Angiogenesis	None	Focal, 1–5 vessels per 20x HPF	3–5 vessels per 20x HPF	6–10 vessels per 20x HPF	≥ 11 vessels per 20x HPF
Proteoglycan/collagen (circumference)	None	≤ 25% of the area stains green-blue/ yellow on Movat	26%–50% of the area stains green-blue/ yellow on Movat	51%–75% of the area stains green-blue/ yellow on Movat	> 75% of the area stains green-blue/ yellow on Movat
Hemorrhage (red blood cells)	None	Focal, occasional	Multifocal and regional	Regionally diffuse	100% red cells
Calcification	None	Focal < 10% of region affected	Multifocal 10%–25% of region affected	Regionally diffuse 26%–30% of region affected	Regionally diffuse > 30% of the region affected

Abbreviations: GC, giant cell; HPF, high-power field.

Following euthanasia, a comprehensive necropsy was performed. The excised SFA specimens were photographed and placed in labeled specimen containers filled with neutral buffered formalin and provided to the histopathology lab (CV Path Institute in Gaithersburg, MD). Histologic sections from all 14 arteries were assessed for healing response criteria that are consistent with known sequelae following femoral artery access and closure procedures, such as occlusion,[9,10] infection,[11] intraluminal thrombi composed of platelets and fibrin,[12] vessel ectasia, dissection, vascular aneurysms, and inflammatory cells.[13-15] The entire length of the arteriotomy site was sectioned such that normal vessel was present on either side of the access site. Pathologists were blinded to the type of access until all pathologic assessments had been performed and summarized.

Study Endpoints

Histopathological evaluation provided comparison of the vascular tissue responses and arterial healing following use of

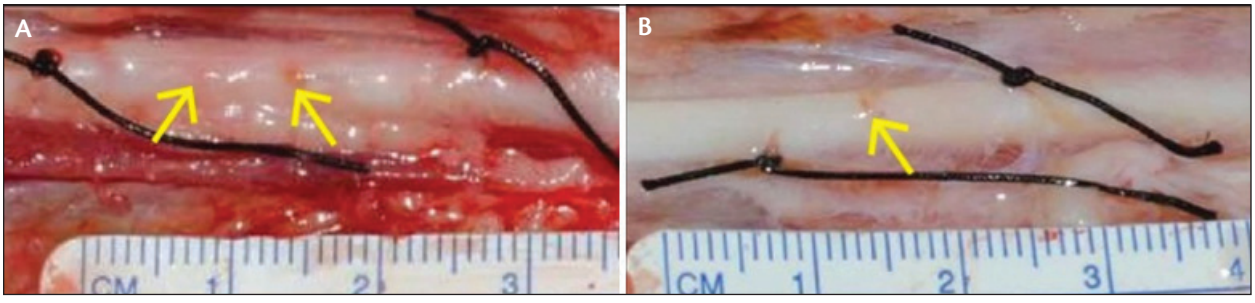

Figure 3. In situ gross images of sheep femoral arteries (animal No. 1979) 30 days after arteriotomy using the AXERA 2 Access System (A) or the modified Seldinger technique (B). Note there was no evidence of laceration, thrombosis, or necrosis. Minor gross lesions (yellow arrows) exhibited small areas with mild adhesions consistent with a healed arteriotomy.

Figure 4. Low-power serial images of left SFA of sheep (animal No. 1979) 30 days after arteriotomy using the modified Seldinger percutaneous access technique (modified Movat pentachrome connective tissue stain). A single transmural puncture wound is seen in panels C to E. There was no evidence of dissection or thrombosis, and hemorrhage is minimal. The wound site is filled mainly by proteoglycan (bluish-green) and smooth muscle cells with neoangiogenesis consistent with the healed arteriotomy. Scale bar: 1 mm.

the modified Seldinger technique and the AXERA 2 Access System. The vascular tissue response and vascular healing were characterized through histopathological analysis of eight parameters (endothelialization [% loss], thrombosis, platelets/fibrin, inflammation, giant cell [GC] reaction, angiogenesis, proteoglycan/collagen, hemorrhage, and calcification). The AXERA 2 device underwent further evaluation. Safety was assessed according to the following criteria: lack of death, access site complication or major access site-related adverse events directly attributable to the deployment of the device. Effectiveness was defined as successful sheath placement and achievement of hemostasis after sheath removal in conjunction with manual or mechanical compression.

Statistical Analysis

Statistical analyses were designed to assess for differences (AXERA 2 System vs. modified Seldinger technique) among the previously mentioned eight histopathological parameters. In each of the seven animals, the left SFA was accessed using the modified Seldinger technique and served as the control, while the right SFA was accessed with the AXERA 2 System with proximal and distal punctures devised as test sites. Thus, a within-animal paired-sample statistical design was used, whereby both proximal and distal AXERA sites were compared to the contralateral control site.

For each access site, histologic samples were assigned multiple ordinal scores using a semiquantified scoring system of 0 through 4 (0 = not identified, 1 = trace, 2 = mild, 3 = moderate, and 4 = severe) for each of the eight parameters assessing the vascular tissue response and healing. An explanation of the semiquantitative grading system employed in the assessment process is shown in Table 1. Ordinal scores were consolidated by three methods: lowest score (minimum), highest score (maximum), and mean. The results for all three methods were consistent. Arithmetic differences (the delta of each AXERA site vs. the control site) were calculated. A single delta was thus obtained for each of the eight parameters for each animal. Statistical analyses were performed using one-sample *t*-tests and corresponding nonparametric Wilcoxon Signed Rank tests.

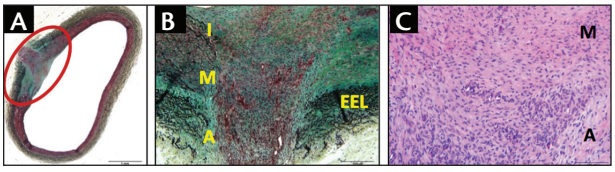

Figure 5. Low- (A) and higher-power histologic images (B, C) of sheep (animal No. 1979) 30 days after arteriotomy using the modified Seldinger percutaneous access technique. A single wound is seen (A, red oval). There was no evidence of dissection or thrombosis, and hemorrhage is minimal. Panel C shows a smooth muscle cell—rich area with neoangiogenesis. A and B are modified Movat pentachrome connective tissue stain; C is hematoxylin and eosin (H&E). Abbreviations: A, adventitia; M, media; I, intima; EEL, external elastic lamina. Scale bar: A = 1 mm, B = 200 µm, and C = 100 µm.

Results

Histological samples included 165 sections from 14 arteries. Sample gross and microscopic images are shown in Figures 3 through 9. The histopathological assessment for the AXERA 2 System evaluated both the more proximal shallow-angle sheath entry site and the distal initial access site. A single puncture site for each animal was evaluated for access achieved with the modified Seldinger technique. There was no indication of vascular aneurysm, vessel ectasia, dissections, or luminal thrombosis associated with either the AXERA 2 System or standard modified Seldinger access. The arteries were widely patent. Vascular healing was characterized by minimal to mild inflammation accompanied by neoangiogenesis near the adventitial medial border. Luminal surfaces were mostly covered by endothelium. There was no indication of fibrin, and giant cells were rare. Mild to moderate calcification mostly involving the medial wall was noted in six arteries (three SFAs from control sites and three from AXERA sites). This was an expected finding, as calcification related to deep arterial injury in the sheep model is consistent with the normal vascular healing response.

Neointimal growth was minimal, and the extent of injury response did not exceed 25% of the lumen circumference

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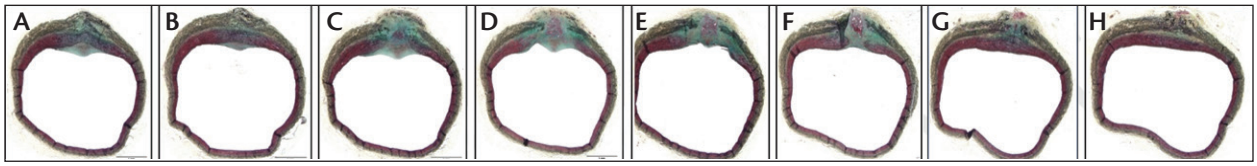

Figure 6. Low-power serial images of the right SFA of sheep (animal No. 1979) 30 days after arteriotomy (distal puncture) using the AXERA 2 Access System (modified Movat pentachrome connective tissue stain). A single transmural puncture wound from the distal site is seen in panels C to F. There was no evidence of dissection or thrombosis, and hemorrhage is minimal. The wound site is filled mainly by proteoglycan (bluish-green) and smooth muscle cells with neoangiogenesis consistent with the healed arteriotomy. Scale bar: 1 mm.

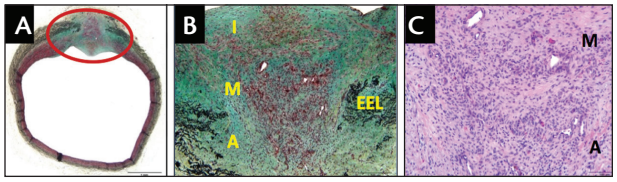

Figure 7. Low- (A) and higher-power histologic images (B, C) of sheep (animal No. 1979) 30 days post arteriotomy (distal puncture site) using the AXERA 2 Access System. A single wound is seen (A, red oval). There was no evidence of dissection or thrombosis, and hemorrhage is minimal. Panel C shows a smooth muscle cell–rich area with neoangiogenesis. A and B are modified Movat pentachrome connective tissue stain; C is H&E stain. Abbreviations: A, adventitia; M, media; I, intima; EEL, external elastic lamina. Scale bar: A = 1 mm, B = 200 µm, and C = 100 µm.

and was generally less (Table 1). The absence of fibrin and complete endothelial coverage indicated an advanced stage of healing for both control and AXERA sites. Injury as seen in histologic sections was mostly confined to the adventitia and media or was transmural, involving the entire artery wall. Noted transmural injury for the most part was confined to three or four levels per injury site. Areas exhibiting transmural injury mostly consisted of accumulated proteoglycan of the medial wall filled in by smooth muscle cells (SMCs) with varying degrees of neoangiogenesis accompanied by surrounding inflammatory cells.

Overall, there was no indication of endothelial cell loss without residual fibrin/platelets. Minimal to mild inflammation consisting of macrophages and fewer numbers of lymphocytes, however, were present, particularly in areas with transmural injury. Hemosiderin-laden macrophages were not uncommon, particularly in areas of transmural injury.

Histopathological assessments suggest no difference in the healing of the arteries. No safety concerns were raised because there were no significant deleterious pathologic chains observed grossly and histologically. Figure 10 presents the 95% confidence intervals of the mean deltas between the distal AXERA 2 access site and the contralateral standard Seldinger control site, and Figure 11 shows the deltas between the proximal AXERA 2 shallow-angle puncture site and the contralateral Seldinger control site. There appeared to be less endothelial loss in the distal AXERA 2 access site and less inflammation of the proximal AXERA 2 shallow-angle micropuncture access site compared to the modified Seldinger technique control. There was no histopathological evidence that would show AXERA 2 leading to worse histopathological results than the modified Seldinger technique.

Ultrasound performed before vascular access revealed a mean SFA arterial diameter of 4.6 mm. Angiography revealed spasm that was observed bilaterally in isolated instances despite use of verapamil and nitroglycerin. Following sheath removal and normal manual compression, no extravasation, hematoma, dissection, or other vascular access site complications were detected with angiography.

Discussion

Despite nearly 60 years of experience with percutaneous access using the modified Seldinger technique, limited data exist regarding the vascular response and arterial healing of the femoral artery. Histopathological analysis was the cornerstone of this investigation assessing the vascular response, arterial access site healing, and safety after use of the modified Seldinger technique and the AXERA 2 device.

Significant results of the analysis include a lack of dissection, luminal thrombus, vascular aneurysm, vessel ectasia, and other differences detected with histopathological analysis for either technique used to obtain access. No safety concerns were evident based on the lack of significant deleterious pathologic changes observed grossly or histologically. Findings from the analysis suggest there were no significant differences in the vascular response and healing between ovine arteries accessed utilizing the modified Seldinger technique or the AXERA 2 device with two exceptions (Figures 10 and 11). For both exceptions (endothelial loss and inflammation), results for the AXERA 2 device were favorable compared to the modified Seldinger technique. The analysis indicates that healthy ovine arteries recover with good overall histopathological findings for healing 30 days after access. No safety concerns were raised from the histopathology.

Endothelial loss and inflammation were the two param-

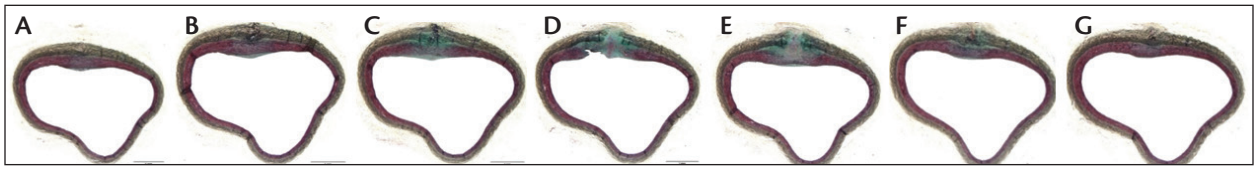

Figure 8. Low-power serial images of the right SFA of sheep (animal No. 1979) 30 days after arteriotomy (proximal puncture) using the AXERA 2 Access System (modified Movat pentachrome connective tissue stain). A single transmural puncture wound is seen in panels D and E. There was no evidence of dissection, or thrombosis, and hemorrhage is minimal. The wound site is filled mainly by proteoglycan (bluish-green) and smooth muscle cells with neoangiogenesis consistent with the healed arteriotomy. Scale bar: 1 mm.

eters demonstrating statistically significant differences between the two access methods. Greater endothelial loss due to placement of a 5-F sheath inserted following modified Seldinger technique access, compared to placement of the 3-F AXERA 2 device at the distal access site, provides a plausible explanation for the difference favoring the AXERA 2 device. Regarding inflammation, the maximum amount of inflammation seen at sites (modified Seldinger technique access and AXERA 2 proximal access) was very minimal. Differences were assessed to be clinically insignificant and may represent biologic variability.

The access site healing comparison is of particular interest because the AXERA 2 device employs a unique approach to postcatheterization access site management by precisely creating a shallow-angle micropuncture of the arterial wall. This shallow-angle puncture helps to attain rapid hemostasis while avoiding the use of implants and their known complications. When the arterial wall is compromised utilizing the 45°-angle Seldinger approach, as the introducer sheath is withdrawn, blood pressure in conjunction with the loss of tension in the artery wall causes the arteriotomy to gape until a hemostatic plug forms. In contrast, with the 10° to 15° shallow-angle approach, the overlapping tissues of the longer access tract in the arterial wall are held in apposition by arterial blood pressure, exerting pressure to close the arteriotomy, and improving the effectiveness of manual compression.

In summary, the increased tissue-on-tissue overlap provided by a shallow-angle arteriotomy produces geometrical advantages resulting in a shorter compression time and less compression intensity,[4] with no evidence of dissection, thrombosis, ectasia, aneurysm, or other untoward events. Histopathological analysis substantiated the safety and efficacy of the AXERA 2 device as compared to the modified Seldinger technique.

Limitations

The healing response in healthy sheep differs from humans with systemic atherosclerosis. Sheep arteries are thinner with a less robust structure, and are free of vascular disease, including calcification that might have significant impact on healing. Thus, the findings from this study cannot be completely extrapolated to the typical catheterization

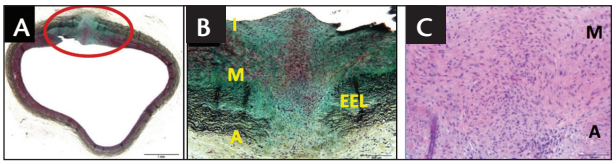

Figure 9. Low- (A) and higher-power histologic images (B, C) of sheep (animal No. 1979) 30 days after arteriotomy (proximal puncture site) using the AXERA 2 Access System. A single transmural puncture wound is seen (A, red oval). There was no evidence of dissection, thrombosis, and hemorrhage is minimal. The wound site is filled in mainly by proteoglycan (bluish-green) and smooth muscle cells with neoangiogenesis consistent with the healed arteriotomy. Panel C shows a smooth muscle cell—rich area with neoangiogenesis. A and B are modified Movat pentachrome connective tissue stain; C is an H&E stain. Abbreviations: A, adventitia; M, media; I, intima; EEL, external elastic lamina. Scale bar: A = 1 mm, B = 200 µm, and C = 100 µm.

patient with diabetes, hypertension, and nicotine abuse. However, for the purposes of the comparison of acute iatrogenic tissue responses related to vascular closure devices with those associated with manual compression, the ovine model represents a reasonable facsimile. Finally, the sample size is small, and the possibility of a type II error remains.

CONCLUSION

Results of this study demonstrate an excellent tissue response following use of the AXERA 2 device in healthy sheep SFA vasculature without any complications or significant adverse events peri- or postprocedure. In addition, results showed no significant difference in healing of the arteries treated with the device as compared to modified Seldinger technique as determined through the majority of histopathological assessments. The analysis demonstrated statistically significant differences for endothelial loss and inflammation between access methodologies, favoring the AXERA 2 device. The arteriotomy created by the AXERA 2 device facilitates hemostasis as arterial blood pressure exerts force against the longer, shallow-angle arteriotomy. As a result of the significantly greater tissue-on-tissue overlap, the amount of occlusive manual compression necessitated by the shallow-angle arteriotomy approach is significantly less

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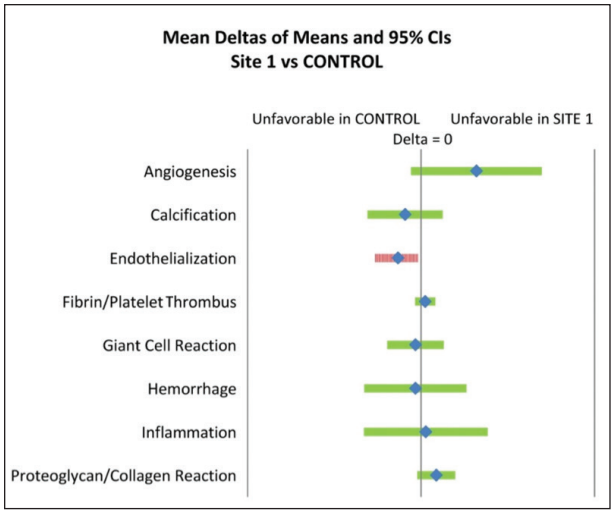

Figure 10. Statistical results of the distal AXERA 2 access (site 1) versus the modified Seldinger technique access (control). Graphic presentation of the 95% confidence intervals (CI) of the mean deltas between the distal AXERA 2 access site and the modified Seldinger technique access site. If the CI intersects the delta = 0 reference line, there is no significant difference at a two-tailed $\alpha = 0.05$ level. Correspondingly, should the CI not cover the delta = 0 line, the results are statistically significant (red hashed line) in the direction indicated by the sign of the delta (negative = control is worse; positive = test is worse). Endothelial loss was unfavorable for the control (modified Seldinger technique) compared to the distal AXERA 2 access site.

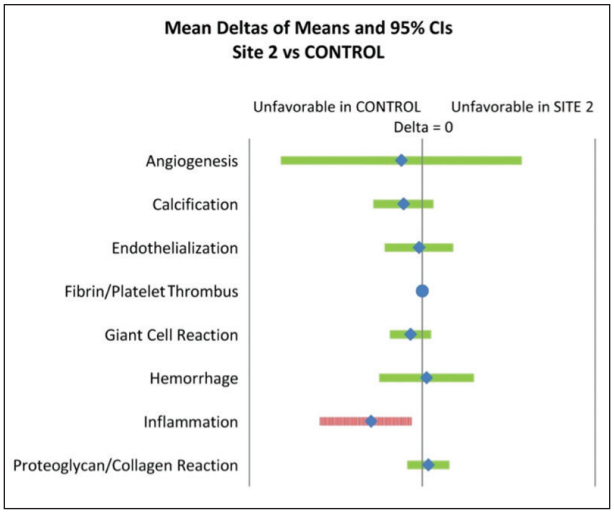

Figure 11. Statistical results of the proximal AXERA 2 access (site 2) versus the modified Seldinger technique access (control). Graphic presentation of the 95% CIs of the mean deltas between the proximal AXERA 2 access site and the modified Seldinger technique access site. If the CI intersects the delta = 0 reference line, there is no significant difference at a two-tailed $\alpha = 0.05$ level. Correspondingly, should the CI not cover the delta = 0 line, the results are statistically significant (red hashed line) in the direction indicated by the sign of the delta (negative = control is worse; positive = test is worse). Inflammation was unfavorable for the control (modified Seldinger technique) compared to the proximal AXERA 2 access site.

than that required after the implementation of the standard modified Seldinger approach.

In summary, the ovine data indicate that the AXERA 2 Access System appears to be as safe as the modified Seldinger percutaneous access technique. Furthermore, these data show that healthy ovine arteries recover with good overall histopathological findings for healing 30 days after access by either methodology. ■

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