CME-Certified Article
Histopathologic Observations of Femoral Closure Devices: Understanding the Differences
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Project ID: 5196 ES13

Target Audience
This activity has been designed to meet the educational needs of cardiologists involved in the management of patients who are undergoing invasive cardiac intervention.

Statement of Need
Successful closure of the femoral artery entry site is an important part of preventing complications and improving healing after catheterization. Arteriotomy closure devices have been widely employed to expedite ambulation in patients undergoing diagnostic coronary angiography or percutaneous angioplasty. Several closure devices are available, and recent comparative studies provide data regarding complications and healing.

Faculty
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Estimated time to complete activity: .5 hours

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Educational Objectives
After completing this activity, the participant should be better able to:
- Describe the acute changes in vascular size that occur in response to the placement of closure devices (vasospasm)
- Identify the acute pathological changes associated with vascular closure (hematoma, inflammation)
- Distinguish the differences in healing late after vascular closure device placement
- Review prior comparative studies

Disclosure
Dr. Bailey is an advisor for Abbott Vascular.

Histopathologic Observations of Femoral Closure Devices: Understanding the Differences

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Arteriotomy closure devices have been widely employed to expedite ambulation in patients undergoing diagnostic coronary angiography or percutaneous angioplasty. As compared with manual compression, these devices decrease time to complete vessel closure, allow earlier ambulation, and improve overall patient comfort. When complications occur, they are often severe and include vascular occlusion, significant bleeding, or inflammatory changes. Animal models have been used to evaluate the impact of these devices. In animal studies, the initial procedure seems to incite mild to moderate vascular spasm that resolves at an undetermined time after the initial procedure. Inflammation occurs early and is most prominent in suture-based and collagen-based procedures compared with extravascular clip procedures. At late time points (after 30 to 60 days), however, no significant differences in angiographic appearance of the vessels could be determined.
[Rev Cardiovasc Med. *2008;9(1):20-28*]

Key words: Coronary angiography • Percutaneous angioplasty • Arteriotomy closure devices • Vascular occlusion

Data regarding the clinical use of arterial puncture closure devices were initially published in 1992 and 1993.[1-3] Since that time, arteriotomy closure devices have been widely employed to expedite ambulation in patients undergoing diagnostic coronary angiography or percutaneous angioplasty. These devices may offer several advantages over manual compression. They have been shown to decrease time to complete vessel closure, allow earlier ambulation, and improve overall patient comfort.[2] Improved resource

utilization has been shown to decrease the costs associated with femoral closure devices.[4-6]

In the last few years, 3 large meta-analyses have been reported. They detail multiple devices used at varying points of maturity and demonstrate that closure devices in general are noninferior to manual compression.[7-9] Three of the commonly used implants for closure of arteriotomies approved by the US Food and Drug Administration are Angio-Seal™ (St. Jude Medical, St. Paul, MN), Perclose® (Abbott Vascular, Santa Clara, CA), and StarClose® (Abbott Vascular, Santa Clara, CA) (Figure 1). Each of these devices has a different mechanism for achieving hemostasis. Angio-Seal deploys a biodegradable collagen plug that dissolves within 60 to 90 days. Perclose uses sutures to close the arteriotomy by tissue approximation. StarClose utilizes a small flexible nitinol clip that provides circumferential, extravascular closure of the femoral arteriotomy site. Individually, all 3 devices have been shown to be clinically noninferior to standard compression with respect to safety endpoints.[10-12] These devices were introduced into clinical practice based upon small studies demonstrating safety of deployment. No cooperative studies were required for approval.

In patients at higher risk—those who are undergoing coronary intervention or who have aggressive anticoagulation—closure devices are reported to have similar complication rates to manual pressure. Complications, when they occur, are often severe and include vascular occlusion, significant bleeding, or inflammatory changes. Acute and chronic inflammation has been reported, as in a case by Doshi and colleagues[13] of a chronic sterile granuloma that developed after Perclose femoral artery closure.

In vivo, randomized studies using hard endpoints to compare the device outcomes have rarely been performed. Additionally, the arterial blood flow, thrombus formation, and histological sequelae resulting from these devices are largely unknown because of the paucity of acute and long-term animal investigations. Knowledge of the vascular changes that accompany each device may aid selection of the device best suited for the particular patient and vessel characteristics.

A compendium of randomized, in vivo studies using animal models is listed in Table 1. An important consideration is that 4 of the 5 investigations used a porcine model for evaluation, and 1 used a canine model. Initial artery injury can result in vasoconstriction, bleeding due to incomplete closure, or thrombus formation. It is unclear if vasospasm is more common in the porcine model than the canine model, but it appears related, in part, to platelet aggregation[14-16] (Figure 2) because it occurs early after vascular access and closure device placement. Extravascular closure seems to have the least impact on spasm after percutaneous closure. There is angiographic confirmation from the animal trials that a thrombus can occur even in normal, nonatherosclerotic vessels, with no associated complications. It should be noted that these animals have robust thrombotic cascades and multiple collaterals that would limit any clinical sequelae. In the porcine model, vasospasm after implantation occurred in the vast majority of cases and was sustained beyond the first several minutes. This result may play an important, although uncertain, role in patients with small femoral arteries or in patients in whom arterial access is achieved in small distal vessels, such as the profunda femoris.

Prior in vivo investigations have demonstrated significant variability in the vascular inflammatory responses among species.[17,18] The canine model has been characterized as ill-suited for evaluation of the inflammatory or

Figure 1. *Perclose system shown in left panel, Angio-Seal STS system shown in center panel, and StarClose system shown in right panel. Perclose and StarClose images courtesy of Abbott Vascular. © 2008 Abbott Laboratories. All Rights Reserved. Angio-Seal STS image courtesy of St. Jude Medical. © 2008 St. Jude Medical. All Rights Reserved.*
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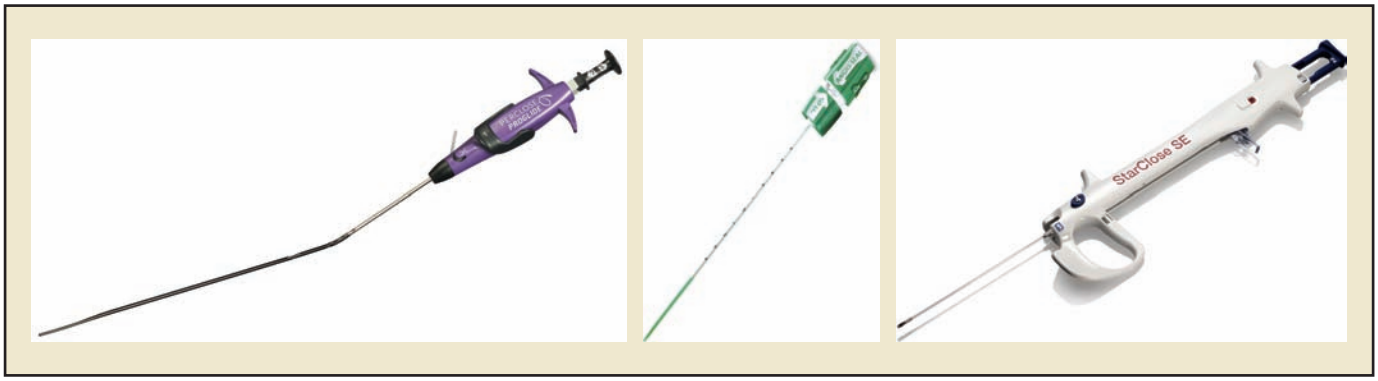


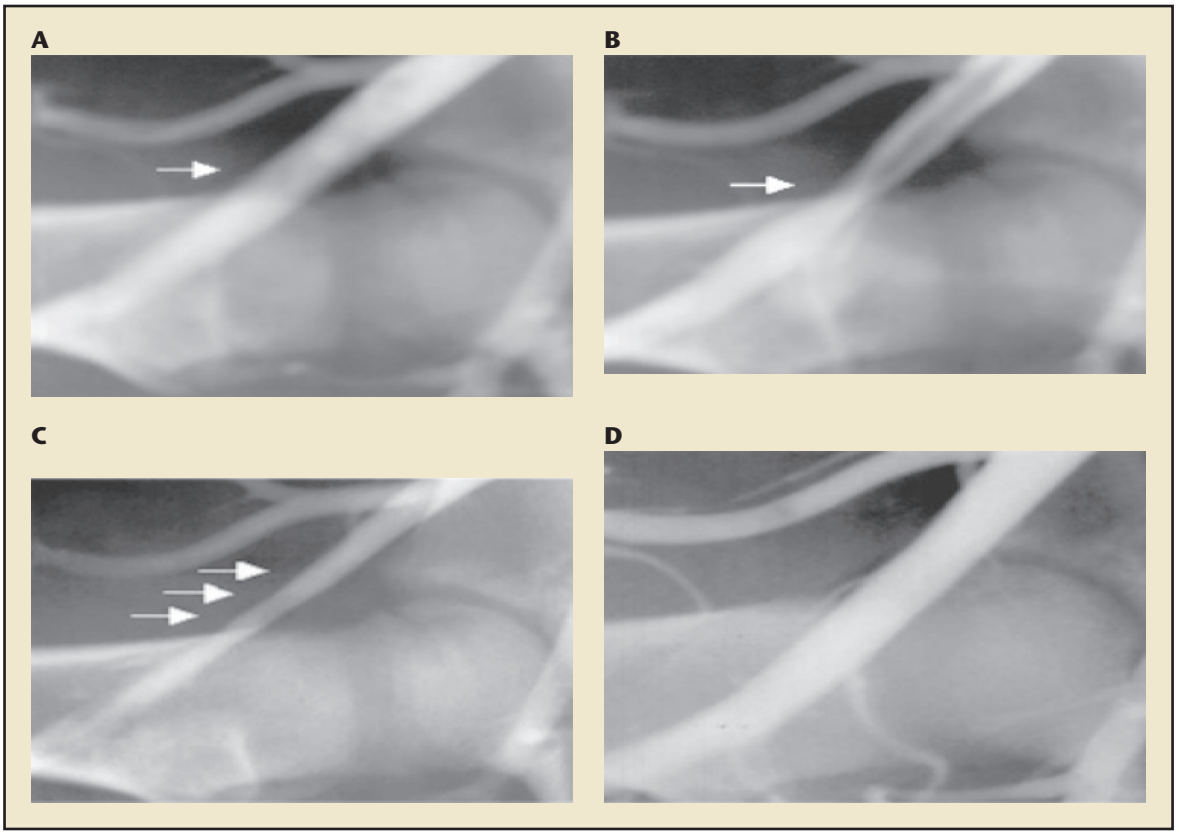
Table 1
In Vivo Studies Evaluating Femoral Closure Devices

Investigator	Year	Animal Model	Systems Evaluated	Conclusion
Leppäniemi A et al[14]	1996	Porcine	Suture vs clip	No benefit of the clips compared with sutures with regard to the development of intimal reactions
Silver FH, Quintero L[20]	2003	Porcine	Collagen vs manual	No difference in inflammation
Gargiulo N et al[12]	2007	Canine	Perclose vs Angio-Seal	Angio-Seal demonstrated greater vessel narrowing and periadventitial inflammation
Sanhgi P et al*	2008	Porcine	Angio-Seal vs clip	Angio-Seal STS system caused more vessel narrowing accompanied by significant histological changes (inflammation and thrombosis) immediately and at 7 and 30 days after device implantation

*Personal communication.

healing response. Dogs have been utilized as an experimental model because of their vessel size, relatively low cost, and availability. The wall of the canine artery and its coagulation system are poorly reactive to mechanical injury. Typically in dogs, injury causes only a thin neointima with limited adventitial fibrosis in the artery. The high fibrinolytic activity of the canine model is markedly different from the diminished porcine response and may be related to the development of restenosis. The development of a fibrin-rich mural thrombus appears to initiate neointima formation by providing a nidus for medial smooth-muscle cell colonization, a mechanism suggested by pig and rabbit models. This mechanism may

Figure 2. *Angiogram of the right common femoral artery.* **(A)** *Before sheath placement, there is no abnormality of the common femoral artery (arrow).* **(B)** *Focal narrowing at the arteriotomy site (arrow) after ultrasonographically guided percutaneous placement of an 8-F sheath.* **(C)** *Segmental narrowing (arrows) of the arterial lumen after deployment of the Sutura device.* **(D)** *No evidence of luminal narrowing on 4-week follow-up angiography. This figure was originally published in the* Journal of Vascular and Interventional Radiology, *Volume 14. Hofmann LV, Sood S, Liddell RP, et al. Arteriographic and pathologic evaluation of two suture-mediated arterial closure devices in a porcine model. Pages 755-761.*[21] *Copyright © Society of Interventional Radiology 2003.* www.medreviews.com



explain why some antiproliferative therapies demonstrate significant inhibition of neointimal hyperplasia in animal models but not in clinical trials. The canine model, with its high fibrinolytic activity, may not generate substantial neointimal volume because it lacks macroscopic thrombus formation. Porcine coronary and peripheral arteries have many properties similar to human vessels and have been used as a surrogate for human interventions. The time course of healing is accelerated as compared with human vessels.

Any investigation must utilize similar degrees of injury or correct the neointimal measurements for the extent of the mural injury. Other factors to be considered in comparing different models include the nature and site of the injury, differences in animal and artery size, and variations in fibrinolytic and thrombolytic capacity. There are studies demonstrating species-specific distinctions in cell proliferation and potency of growth factors.

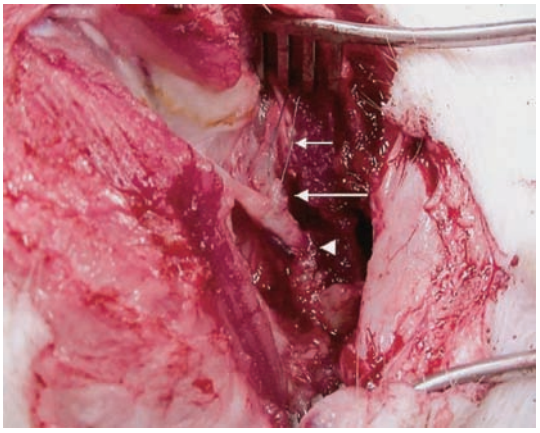


Figure 3. *Gross picture of typical in situ fibrous hood (long arrow) surrounding the Perclose sutures (short arrow). Arrowhead denotes the common femoral artery. This figure was originally published in the* Journal of Vascular and Interventional Radiology, *Volume 14. Hofmann LV, Sood S, Liddell RP, et al. Arteriographic and pathologic evaluation of two suture-mediated arterial closure devices in a porcine model. Pages 755-761.*[21] *Copyright © Society of Interventional Radiology 2003.* www.medreviews.com

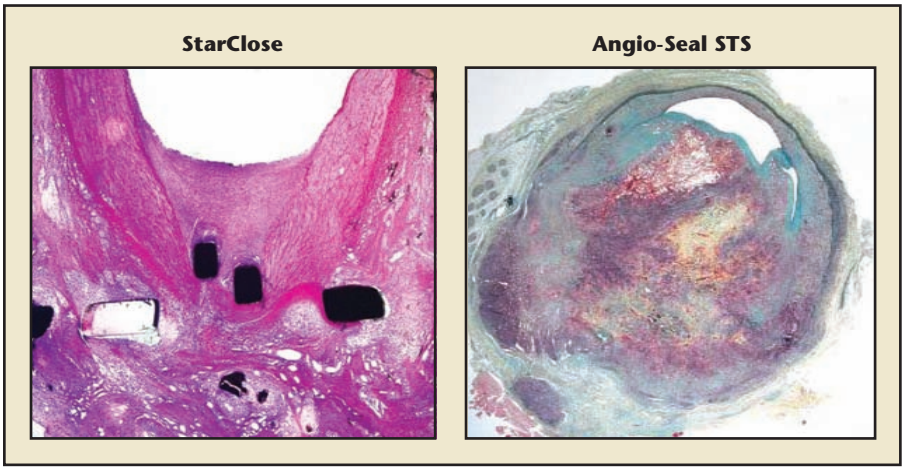
Any investigation must utilize similar degrees of injury or correct the neointimal measurements for the extent of the mural injury.

Recent studies have highlighted some of these issues. Hofmann and colleagues[19] demonstrated extravascular inflammation at the closure site (Figure 3). Unfortunately, this study did not quantitate the degree of inflammation. Recently, my colleagues and I evaluated early and late histopathologic changes in a porcine model. In this study, 19 pigs underwent bilateral arteriotomies that were closed with either Angio-Seal STS Plus or StarClose. Angiograms and ultrasounds of the site were performed before closure and immediately after. At follow-up, ultrasound was performed at the site, and specimens were sent for histopathology. Angio-Seal was associated with more immediate vasospasm and more vessel injury than StarClose (Figure 4). We quantitated the inflammatory component of the arteriotomies at 7 and 28 days and found that the Angio-Seal STS Plus was associated with higher percentages of inflammation, hemorrhage, and vessel stenosis or thrombosis (Figure 5). This effect was resolved by the 60-day follow-up examination. In the study by Hofmann and colleagues,[19] the suture-based treatments created chronic inflammatory responses that persisted at 30 days. However, this small, short-term study employed older generation devices in arteries that were smaller than those designated by the directions for use.

Conclusions

Few randomized controlled studies have been conducted in animal models to investigate the healing response after percutaneous femoral closure. The majority of the studies to date have occurred in nonatherosclerotic

Figure 4. *Representative histology of the StarClose and Angio-Seal STS devices at 30 days.* www.medreviews.com



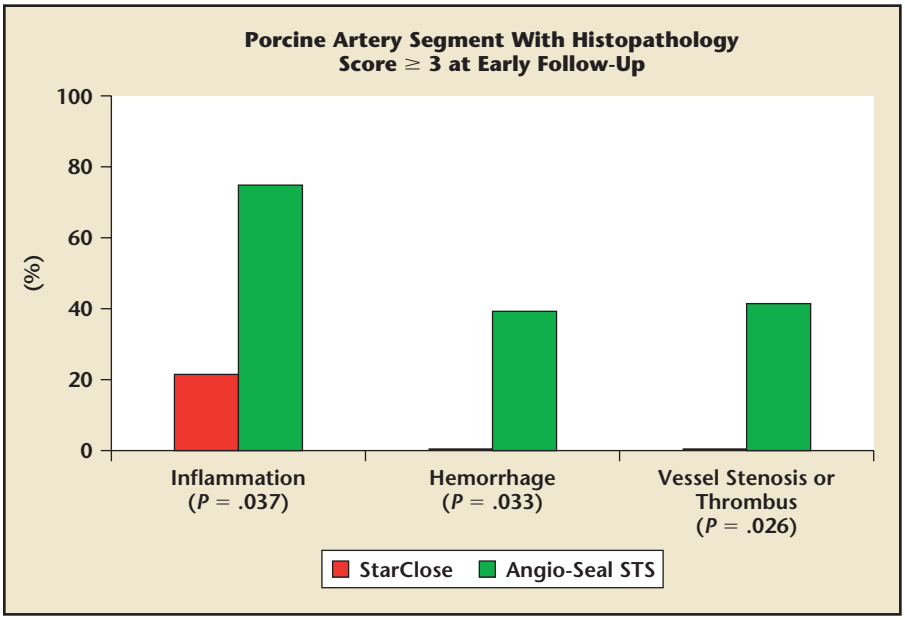


Figure 5. *Comparison of vessels with high inflammatory counts (> 101 inflammatory cells per 40 × high-powered field) after StarClose or Angio-Seal STS implantation at 7 and 30 days.* www.medreviews.com

swine femoral arteries. The initial procedure seems to incite mild to moderate vascular spasm that resolves at an undetermined time after the initial procedure. Inflammation occurs early and is most prominent in the suture-based and collagen-based procedures compared with the extravascular clip procedures. At late time points (after 30 to 60 days), however, no significant differences in angiographic appearance of the vessels could be determined. The inflammation may continue for an undetermined period of time but seems to be similar at the late time points. ■

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Main Points

- Arteriotomy closure devices are widely employed to expedite ambulation in patients undergoing diagnostic coronary angiography or percutaneous angioplasty.
- As compared with manual compression, arteriotomy closure devices decrease time to complete vessel closure, allow earlier ambulation, and improve overall patient comfort.
- Complications associated with arteriotomy closure devices include vascular occlusion, significant bleeding, or inflammatory changes.
- In animal studies, inflammation occurs early and is most prominent in suture-based and collagen-based devices compared with extravascular clip devices.
- At late time points (after 30 to 60 days), the angiographic appearance of the vessels appears similar with both the suture-based and collagen-based devices and the extravascular clip devices.

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SELF-ASSESSMENT POST-TEST

Histopathologic Observations of Femoral Closure Devices: Understanding the Differences

1. Initially, vascular reactions to invasive procedures, such as diagnostic coronary angiography or percutaneous angioplasty, include:
   a. mild to moderate vascular spasm
   b. inflammation
   c. a and b

2. Advantages of arteriotomy closure devices include:
   a. earlier ambulation
   b. improved patient comfort
   c. decreased time to complete vessel closure
   d. decreased cost
   e. all of the above

3. Higher risk patients, who may be anticoagulated or undergoing coronary intervention, have _____ rates of complications with vascular closure devices compared with manual compression.
   a. higher
   b. lower
   c. about the same

4. Initial arterial injury can result in:
   a. vasoconstriction
   b. bleeding due to incomplete closure
   c. thrombus formation
   d. all of the above

EVALUATION FORM

Histopathologic Observations of Femoral Closure Devices: Understanding the Differences
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To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. ***You must complete this evaluation form to receive acknowledgment for completing this activity.***

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES

After completing this activity, I am now better able to:

- Describe the acute changes in vascular size that occur in response to the placement of closure devices (vasospasm) 1 2 3 4 5
- Identify the acute pathological changes associated with vascular closure (hematoma, inflammation) 1 2 3 4 5
- Distinguish the differences in healing late after vascular closure device placement 1 2 3 4 5
- Review prior comparative studies 1 2 3 4 5

OVERALL EFFECTIVENESS OF THE ACTIVITY

The content presented:

- Was timely and will influence how I practice 1 2 3 4 5
- Enhanced my current knowledge base 1 2 3 4 5
- Addressed my most pressing questions 1 2 3 4 5
- Provided new ideas or information I expect to use 1 2 3 4 5
- Addressed competencies identified by my specialty 1 2 3 4 5
- Avoided commercial bias or influence 1 2 3 4 5

IMPACT OF THE ACTIVITY

Name one thing you intend to change in your practice as a result of completing this activity: _____

_____

Please list any topics you would like to see addressed in future educational activities: _____

_____

Additional comments about this activity: _____

_____

FOLLOW-UP

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

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❒ No, I am not interested in participating in a follow-up survey.

POST-TEST ANSWER KEY

1_____ 2_____ 3_____ 4_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and FAX to: 303-790-4876.

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