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Hemostasis: Can We Do Better Than the Gold Standard?

Vascular closure devices can provide reliable and safe hemostasis at the arteriotomy site.

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Achieving hemostasis in patients after catheterization is crucial for the overall success of coronary or vascular catheterization. Manual compression is still considered the gold standard for controlling bleeding at the arteriotomy site in the majority of hospitals around the world. Although this approach of applying physical pressure at the puncture site does stop bleeding, its effectiveness relies on the body's coagulation cascade to do most of the work. With the addition of chemical factors that promote coagulation and hemostasis, the coagulation cascade can be facilitated, resulting in shorter times to hemostasis and ambulation.

This article reviews the physiology and biochemistry of the coagulation cascade, detailing the body's response at the arteriotomy site after catheterization. We further review the effects of manual compression on this response, as well as vascular closure devices (VCDs) that are developed to facilitate postprocedure hemostasis, either by direct occlusion of the arteriotomy site, by inducing and supporting the activation of the coagulation cascade, or by a combination of these two mechanisms. Finally, we examine the effects of negatively and positively charged chemical coatings on the Boomerang Catalyst™ II System (Cardiva Medical, Inc., Mountain View, CA) to describe the effects these substances have on the coagulation cascade.

METHODS OF ACHIEVING ACCESS-SITE HEMOSTASIS

The overall success of catheterization procedures, especially coronary and vascular interventions, depends very much on achieving secure hemostasis. Vascular access complications have been associated with substantial morbidity and mortality rates.[1,2] Manual compression does not require costly devices, has a good safety profile (with a very long experience of more than 50 years since Seldinger's description), has a short learning curve, does not leave a foreign body at the arteriotomy site, and is therefore still regarded as the gold standard for controlling bleeding at the arteriotomy site in the majority of hospitals around the world. Although applying physical pressure at the puncture site leads to hemostasis, its effectiveness relies on the body's coagulation cascade. Manual compression is not a comfortable procedure for the patient and the medical staff; it requires time, and it can slow the throughput of the recovery area and the catheterization laboratory. It is associated with possible hypotension and bradycardia due to vagal reaction during the compression, as well as complications after the compression, including hematoma, pseudoaneurysm, arteriovenous fistula, retroperitoneal hematoma, and limb ischemia. With the addition of chemical factors that promote coagulation, clotting, and hemostasis, the coagulation cascade can be initiated and augmented, resulting in shorter times to hemostasis and ambulation.

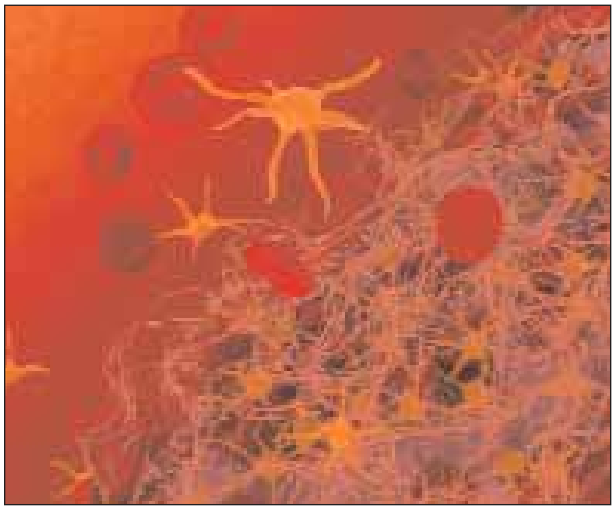

Figure 1. Platelet activation.

Compared to the tremendous resources invested in the development of interventional devices, such as new stent platforms, it was not until approximately 10 years ago—after the introduction of new VCDs—that device-

based hemostasis became the current standard practice in many hospitals. The primary goal was to improve patient comfort and reduce the time to hemostasis, as long as the safety profile was comparable to manual compression. The widespread use of VCDs has enabled hospitals to reduce the time to discharge after catheterization, to increase recovery area throughput, to accept late cases, and to decrease personnel costs if the hospital is at capacity. The medical personnel responsible for the access-site management have usually regarded these changes very favorably. Parallel to the development of improved next-generation VCDs, the hypothesis of a possible reduction of vascular complications with the usage of VCDs has been raised. Most VCDs generally fall into the following categories:

- Sealant-based (collagen and gelatin)
- Suture-mediated
- Staple-based
- Patches
- Assisted manual compression

The decisions regarding the use and the type of VCDs are made on a case-by-case basis, usually after evaluation of the femoral angiogram obtained during the catheterization. For uncomplicated diagnostic and interventional cases, the majority of the arteriotomy sites can be closed using the available VCDs with a high success rate and a very low complication rate.[2,3] For patients with disease and flow-limiting stenoses at the arteriotomy site or with an increased infection risk, such as diabetes, previous valve replacement, or ongoing overt infections, manual compression remains the approach of choice for achieving hemostasis.

The recent introduction of the Boomerang Catalyst II System offers another possibility for "jump starting" the coagulation cascade, especially in patients with complicating conditions without implanting a permanent foreign body. The Boomerang temporarily seals the arteriotomy site, enabling tissue tract recoil, as well as facilitating the coagulation cascade due to two proprietary coatings that activate the intrinsic and extrinsic coagulation cascade pathways.

Once this coagulation response is activated, the Boomerang is completely removed, leaving nothing behind. The average manual compression time can be reduced significantly, and the patient's recovery is accomplished with less strain on both the patient and catheterization laboratory staff.

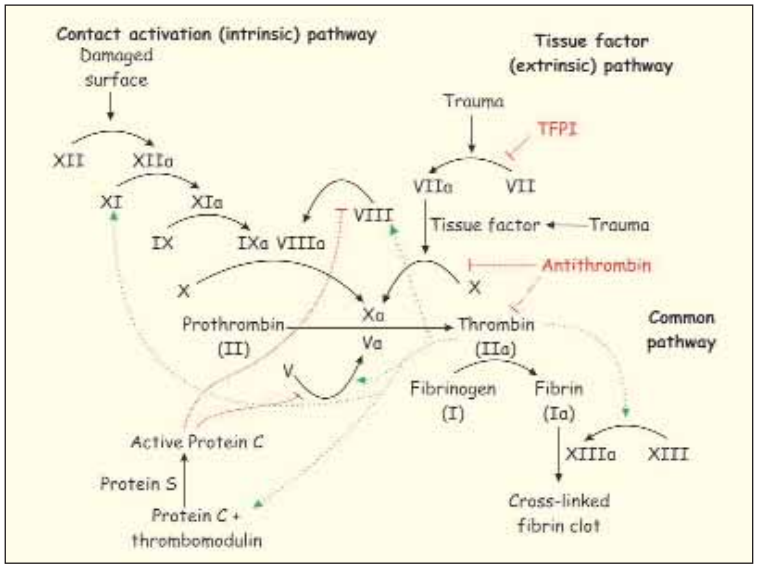

Figure 2. The coagulation cascade of secondary hemostasis has two pathways: the contact activation pathway (formerly known as the intrinsic pathway) and the tissue factor (TF) pathway (formerly known as the extrinsic pathway). The main role of the TF pathway is to generate a thrombin burst. These pathways merge, leading to fibrin formation.

THE COAGULATION CASCADE

To understand how the coatings on the Boomerang Catalyst II System work with the body's natural response to the arteriotomy puncture, it is important to understand the unaided coagulation cascade mechanism. Under normal conditions, the endothelial cell lining of the blood vessels are devoid of hemostatic activators and, in fact, synthesize several anticoagulant agents to keep blood flowing clot-free. After an arteriotomy or vascular injury, however, the endothelial layer is disrupted, and collagen is exposed at the puncture site, leading to platelet activation and a series of enzyme reactions called the *coagulation cascade*. Hemostasis occurs because this series of physiological responses to blood vessel disruption balance the body's need to stop excessive blood loss at the arteriotomy site while at the same time maintaining viable blood circulation throughout the body. The need to stop blood loss requires a coagulation response, whereas the need to maintain circulation requires blood to be in an uncoagulated state. The coagulation response results in the formation of a hemostatic plug, consisting of platelets and fibrin, which blocks the injury site and staunches bleeding.

In the initial response to an arteriotomy, the vessel constricts to minimize blood loss and slow local blood flow at the puncture site. Negatively charged collagen is exposed from the disrupted vessel lining and promotes blood platelets to adhere to the site within 15 to 20 sec-

onds after exposure. Normally, these platelets circulate freely suspended in plasma. At the site of vascular lesions, circulating von Willebrand factor binds to the exposed collagen, which subsequently binds fast, but transiently, to the glycoprotein (GP) Ib/IX, and slower, but with more stability, to GP VI and to receptors on the platelet membrane.[4] After degranulation, platelet-derived adenosine diphosphate (ADP), platelet activating factor, and serotonin (5-hydroxytryptamine, called *5HT*) stimulate adjacent platelets, further enhancing the process of platelet aggregation through the contact activation (intrinsic) and TF (extrinsic) pathways. The coagulation cascade is initiated when blood plasma comes in contact with the exposed endothelial tissue, causing intrinsic platelet proteins to activate chemicals that anchor them to the negatively charged surface. The main role of the TF pathway is to trigger a local burst of thrombin, initially leading to additional stimulation of the platelets at the puncture site. Arachidonate, which is released from the platelet membrane by the stimulatory effect of collagen, thrombin, adenosine diphosphate, and 5HT, promotes the synthesis of thromboxane A2 by the sequential effects of cyclo-oxygenase and thromboxane synthase. Thromboxane A2 not only promotes further platelet aggregation but is also a potent vasoconstrictor.

After platelets adhere to the arteriotomy site, they change shape from smooth spheres to spiny globes with protruding receptors (Figure 1), leading to the previously described degranulation and release of mediators. The effects of these biochemicals cause increasingly more platelets to aggregate and degranulate at the arteriotomy site, forming an initial platelet plug as quickly as 3 to 5 minutes after the introducer sheath is removed.

The TF pathway, previously known as the extrinsic

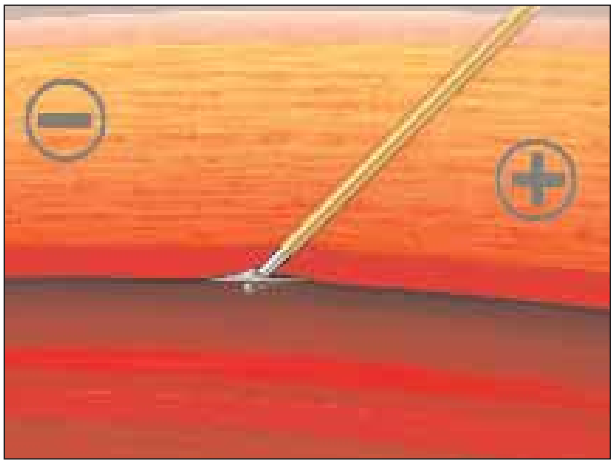

Figure 3. The Boomerang Catalyst II System stimulates contact activation pathway.

coagulation pathway, induces the formation of factor Xa through the TF-factor VIIa complex in the presence of Ca2+ (Figure 2). A second TF-dependent reaction catalyzes the transformation of IX into IXa. Other cofactors include factor VIIIa, which binds to platelets and forms the binding site for IXa, thereby forming the machinery for the activation of X and factor Va, which binds to platelets and provides a binding site for Xa. In physiologic conditions, no cells in contact with blood contain active TF.

Activated Xa converts prothrombin into thrombin. The complex that catalyzes the formation of thrombin consists of factors Xa and Va in a 1:1 complex. The interaction of the four components of the prothrombinase complex (Xa, Va, phospholipid, and Ca2+) enhances the efficiency of the reaction.

Activated platelets provide a procoagulant surface, leading to the activation of factor X to factor Xa and prothrombin to thrombin. The binding of IXa and Xa is promoted by VIIIa and Va, respectively, such that Va, and likely VIIIa, provide the equivalent of receptors for the proteolytic enzymes. The catalytic transformation of fibrinogen into fibrin is essential in the formation of the hemostatic plug. Thrombin acts on multiple substrates, including fibrinogen, factors XIII, V, and VIII, and protein C, in addition to its effects on platelets. It plays a central role in hemostasis and thrombosis. Thrombin binds to the fibrinogen central domain and cleaves fibrinopeptides A and B, resulting in the formation of fibrin monomer and polymer formation. The fibrin mesh, further stabilized by factors XIII, holds the platelets together and contributes to the attachment of the thrombus to the vessel wall.

In summary, blood coagulation occurs when thrombin released through the TF pathway converts soluble plasma fibrinogen to an insoluble fibrin polymer mesh at the arteriotomy site to reinforce the platelet plug. Red blood cells and more platelets become caught in this mesh, forming a clot.

After the clot forms at the arteriotomy site, it solidifies and retracts in the final stage of hemostasis. A contractile protein in the trapped platelets causes fibrin strands in the clot to shorten, forming a stronger seal over and at the edges of the wound. This protein also causes the fibers to stabilize in their strengthened state, completely stopping the flow of blood from the injury site. Clot retraction begins within a few minutes after the clot is formed; the clot is stabilized 60 to 90 minutes after hemostasis is achieved.

Once that clot is formed and hemostasis is achieved, the coagulation cascade must be stemmed to prevent continued clotting and vessel blockage. Three natural

anticoagulant biochemicals regulate this process: antithrombin (ATIII) formed in the liver and vitamin K-dependent inhibitory cofactors, proteins C and S, which are activated by thrombin. Calcium and vitamin K are two substances required for the proper functioning of the coagulation cascade. If platelets would continue to adhere to vessel walls in an uncontrolled fashion, blood circulation to the rest of the body would be compromised. To control the platelet response, endothelial cells lining the blood vessel also release prostaglandin I2, which causes blood vessels to dilate, inhibiting platelet degranulation, and discouraging platelets from adhering to blood vessel walls other than at the puncture site.

Eventually, the clot is broken down (lysis) and is reabsorbed into the blood stream as small clots that are cleared by intravascular enzymes of the thrombolytic system or removed in the kidney and liver. As the main clot is broken down, plasminogen enters the clot and is converted to plasmin, leading to breakdown of the clot's protein fibers. A balance of thrombin and plasmin levels in the blood stream maintains normal clot coagulation, lysis, and clearance.

Factors Affecting Hemostasis

Hemostasis is regulated by the complex interplay of endothelial cell lining in the blood vessel walls, by platelets, and the balance of the prothrombotic coagulation cascade system and the thrombolytic plasminogen system. Excessive bleeding can result from an increased fragility of vessels, platelet deficiency or dysfunction, derangement of coagulation balance, or a combination of these. Coagulation disorders can also lead to excessive clotting and emboli.

The standard vascular access management technique to achieve hemostasis is manual compression to the arteriotomy site for 15 to 30 minutes after removal of the introducer sheath, followed by application of a dressing and maintaining the patient immobile for typically 90 to 240 minutes until full retraction of the clot.

Strain on the vessel wall due to high blood pressure or movement of the patient might disrupt the newly formed clot at the access site, requiring additional compression. Health conditions can also affect a patient's time to hemostasis. Older patients or patients with heart, liver, or kidney conditions might experience disturbances of the clotting process. Patients on dialysis have impaired coagulation and platelet adhesion, and they are likely to have slower clearing of drugs and other agents from their blood, which will impact the coagulation process. Diabetic patients or patients with inflammatory conditions, compromised immune systems, or blood disorders (eg, leukemia) will require longer times to achieve hemostasis.

Drugs that can affect hemostasis include nonsteroidal anti-inflammatory drugs (eg, ibuprofen), antibiotics, anticoagulants (eg, warfarin, enoxaparin), antiplatelet drugs (eg, aspirin, clopidogrel), thrombolytic agents (eg, reteplase), cardiovascular drugs, steroids (eg, asthma medications), tranquilizers, and psychotropic medications. Food additives, leading to absolute or relative vitamin K deficiency, can also affect hemostasis.

VCDs

VCDs can be grouped according to their mode of action as (1) sealant-based, (2) suture-mediated, (3) clip-based, (4) patches, and (5) other novel technologies with assisted manual compression, such as TheraSeal (Therus, Seattle, WA) and Boomerang.

Sealant-Based

The first VCD in the US was approved by the FDA in 1995. This device, the VasoSeal (Datascope Corporation, Mahwah, NJ), is a sealant-based VCD that has been associated with increased complication rates in recent studies.[5] The closure mechanism is based on a collagen plug, which is deployed at the arteriotomy site, occluding it directly and activating the coagulation. The plug is not otherwise secured at that site, and dislodgement of the plug can lead to bleeding. The introduction of Angio-Seal (St. Jude Medical, St. Paul, MN), a very reliable sealant-based VCD with a very good safety profile, has led to a marked increase of VCD usage.[5] The collagen plug, which is anchored by an intravascular foot, achieves mechanical sealing of the arteriotomy and, at the same time, promotes the adhesion of platelets and the activation of the coagulation cascade. The result is reliable closure and markedly decreased bleeding from the tissue tract.

Suture-Mediated

The suture-based VCDs such as the SuperStitch (Sutura, Inc., Fountain Valley, CA), X-Press (X-Site Medical, Blue Bell, PA), and Perclose (Abbott Vascular, Santa Clara, CA) imitate the surgical approach of closure. They offer the advantage of leaving minimal residual suture material, which is absorbed over time, and therefore allow good reaccess options and theoretically less infection risks. Their use has grown over time, especially after the simplification and miniaturization of the Perclose ProGlide device (Abbott Vascular).

Clip-Based

Clip-based devices, such as the Angiolink Vascular Closure System (Medtronic, Inc., Santa Rosa, CA) and StarClose (Abbott Vascular), provide reliable hemostasis,

even for patients with peripheral vascular disease and arteriotomy sites below the common femoral artery bifurcation. The all-metallic clip might have a lower infection risk, but remains permanently at that site.[5] The lack of an activator of the coagulation cascade, such as the collagen in the plug of the Angio-Seal device, leads to more frequent oozing from the tissue tract for both suture- and clip-based devices.

Patches

Overall, the main disadvantages of sealant-, suture-, and clip-based devices are that they rely on mechanical closure with possible disruption of intravascular plaques or damage to the vessel, and introduction of a foreign body with increased potential for infection. Patches, such as the Syvek (Marine Polymer Technologies, Danvers, MA), Duett Pro (Vascular Solutions, Inc., Minneapolis, MN), and Chito-Seal (Abbott Vascular), do not have these disadvantages, but they are used topically and rely on the remote activation of the coagulation cascade from the skin surface.

THE BOOMERANG CATALYST II SYSTEM

The Boomerang Catalyst II System is designed for use with manual compression to facilitate both the intrinsic and extrinsic coagulation cascades, thereby reducing the duration of manual compression. The device is introduced directly after catheterization through the sheath. The nonthrombotic, low-profile, flexible nitinol disc is opened inside the vessel and brought back to the arteriotomy site parallel to the sheath removal, sealing the arteriotomy site temporarily and enabling tissue tract recoil and activating the coagulation cascade.

The surface of the Boomerang Catalyst II Wire, directly adjacent to the arteriotomy site and tissue tract, is negatively charged to further stimulate the contact activation (intrinsic pathway) response and encourage platelet adherence at the site (Figure 3). When factor XII comes in contact with a negatively charged surface, such as the coating on the Catalyst II Wire, it undergoes an auto-activation step, which converts the inactive XII to the active-form XIIa. By encouraging this rapid coagulation response through the intrinsic pathway, the Boomerang Catalyst II "jump starts" the patient's coagulation cascade, causing fibrin to be formed more quickly and hemostasis to be achieved more effectively. The Boomerang Catalyst II Wire's coating also includes a positively charged chitosan compound that has been shown to enhance platelet adhesion and aggregation through the TF (extrinsic) pathway.[6] The interaction between the chitosan coating and exposed subendothelial tissue promotes platelet spreading and strengthens the stability of the aggregated platelets, promoting wound healing. It therefore combines materials such as kaolin and chitosan, which have a long record for providing reliable induction of the coagulation cascade, with the new technology of the Boomerang Wire, enabling the application of coagulation-promoting agents directly at the arteriotomy site and to the tissue tract.

The Boomerang Catalyst II System can also be used to close arterial access sites safely for patients with aortic stenosis after right and left heart catheterization with planned aortic valve replacement, even in the presence of atherosclerosis at the arteriotomy site. If the valve replacement surgery is performed soon after cardiac catheterization, the introduction of a foreign body by most VCDs might not be desirable, increasing the overall risk of prosthetic valve infection. The arterial sheath can be replaced first with the Boomerang device and left in place while the patient is transported to the recovery room. The device is then removed, and 5 minutes of manual compression is applied on the arterial site. The device combines the safety of manual compression, the gold standard, with reduced times to hemostasis and increased comfort for patients and medical staff.

CONCLUSION

The impressive development of vascular closure technology—providing reliable and safe hemostasis of the arteriotomy site tailored to the requirements for specific patient populations—certainly proves that we can do better than the gold standard. ■

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