

A Novel Vascular Sealing Device for Closure of Percutaneous Arterial Access Sites

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The purpose of this study was to investigate the safety and efficacy of a novel vascular sealing device that incorporates a unique low-profile balloon-positioning catheter and a procoagulant delivered after diagnostic cardiac catheterization and percutaneous transluminal coronary angioplasty (PTCA) procedures. Current management of the vascular access site after percutaneous interventions is associated with patient discomfort and complications. Based on previously reported successful results in canine models, we proceeded with this first human feasibility and safety study. Immediately after an invasive procedure, the sealing device was successfully deployed at the femoral arterial access site in 24 of 24 procedures (diagnostic 19, PTCA 5). All patients were followed up at 1 month with clinical assessment, ankle-brachial index measurement, and Doppler ultrasound. Successful hemostasis was achieved in all patients. The

activated clotting time before sealing device deployment was 125.5 ± 22.2 and 267.8 ± 60.0 seconds for diagnostic and PTCA patients, respectively. The time to hemostasis was 2.5 ± 0.9 minutes for diagnostic and 6.0 ± 2.2 minutes for PTCA patients. No major complications were observed. Coagulation markers (fibrinogen, D-dimer, thrombin-antithrombin-3 complex, and prothrombin fragment 1 and 2) measured before and after sealing device deployment did not reveal excessive intravascular thrombin generation or other coagulopathy. This novel vascular sealing device successfully achieves safe and effective vascular access site hemostasis immediately after cardiac catheterization and PTCA. These promising first human results will need to be confirmed by a multicenter randomized trial.

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Conventional techniques of vascular access site management that include manual pressure, vascular clamps, and external inflatable compressors are associated with significant patient discomfort and prolonged bed rest. Several new approaches have been developed to achieve more rapid hemostasis at the arterial access site.¹⁻¹¹ Recently, a novel vascular sealing device has been developed that incorporates a unique low-profile balloon-positioning catheter in combination with a biologic procoagulant mixture containing bovine microfibrillar collagen and thrombin. Collagen is a potent platelet-activating substrate.¹² Thrombin promotes effective hemostasis through several mechanisms. It converts fibrinogen to fibrin, accelerates the coagulation cascade, and is a powerful platelet-activating agent acting synergistically with collagen.¹³ In addition, thrombin promotes tissue healing through its direct actions on monocytes and smooth muscle cells.¹³ In our previously reported preclinical studies, this novel sealing device was able to achieve rapid and reliable hemostasis in a canine model regardless of sheath size or degree of anticoagulation.¹⁴ This report describes the results of the first human feasibility study using this new vascular

sealing device after diagnostic cardiac catheterization and coronary angioplasty procedures.

METHODS

The investigational protocol was approved by the International Ethics Committee of Freiburg, Germany. All patients gave informed consent in accordance with the Declaration of Helsinki. The study was a prospective single-site investigation in consecutive patients undergoing a diagnostic cardiac catheterization or percutaneous transluminal coronary angioplasty procedure.

Exclusion criteria were age >75 years, sheath size of >9Fr, preexisting large hematoma (>6 cm in diameter), severe peripheral vascular disease (resting ankle-brachial index <0.7), coagulopathy or activated clotting time >300 seconds immediately before device deployment, use of abciximab within the past 7 days, recent myocardial infarction (<7 days), uncontrolled hypertension (systolic blood pressure >160 mm Hg, diastolic blood pressure >95 mm Hg), women known to be pregnant, life expectancy of <1 year, and a known allergy to bovine products. All other patients underwent treatment with the sealing device immediately after completion of the antecedent cardiac catheterization procedure.

The sealing device consists of 2 components: a balloon-positioning catheter and an injectable procoagulant (Duett; Vascular Solutions, Minneapolis, Minnesota). The balloon catheter sealing device (Figure 1) is a low-profile catheter (approximately 3Fr) incorporating a moveable core wire that allows in vivo modifications of the balloon dimensions. When the device

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FIGURE 1. The inflated balloon catheter sealing device is shown with the polymeric sleeve retracted. The moveable core wire has been advanced. The procoagulant is shown in a 10-ml syringe.

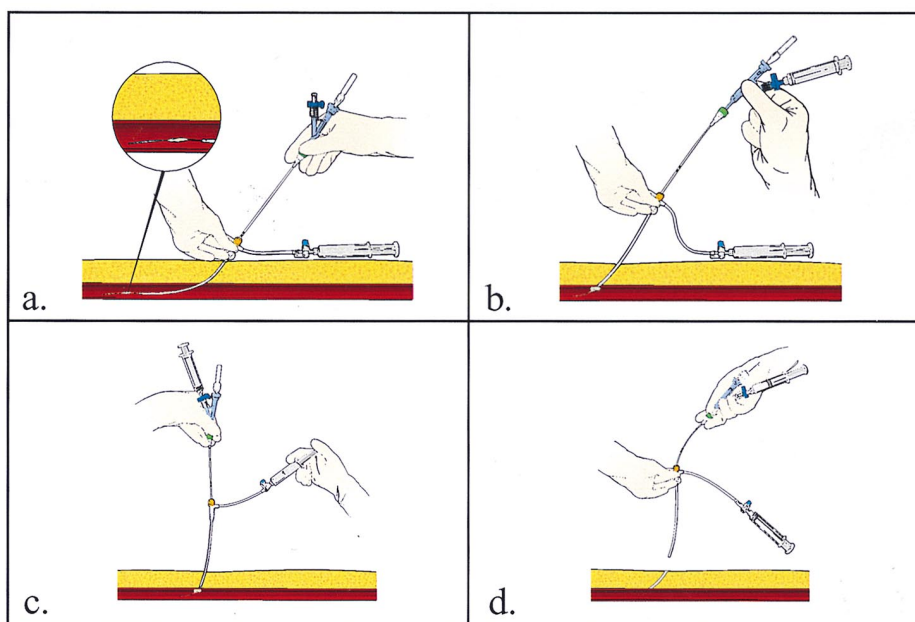
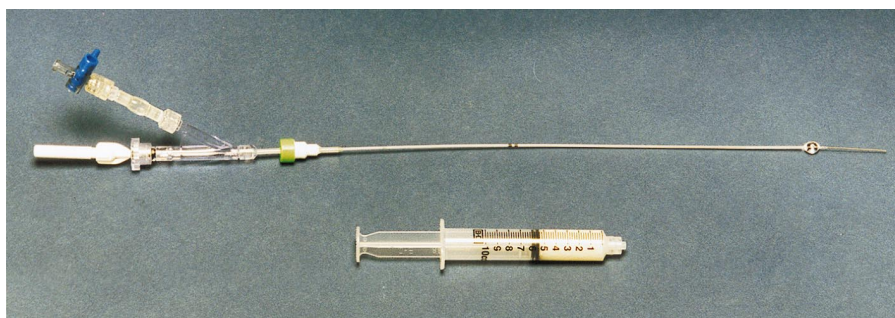


FIGURE 2. *a.*, schematic diagram depicting the balloon-positioning catheter inserted through a conventional vascular introducer sheath. The deflated balloon and atraumatic guidewire tip are shown in the artery just distal to the sheath (*inset*). *b.*, the balloon is inflated and deployed in apposition to the arterial puncture site at the luminal side. The balloon functions as a temporary hemostatic seal, puncture locator, and backstop during injection of the procoagulant; *c.*, the procoagulant is injected through the sidearm of the vascular introducer sheath and exits proximal to the balloon, thereby filling the periarterial extravascular space. Gentle traction is maintained on the balloon catheter during procoagulant injection; *d.*, the balloon catheter has been deflated and removed, with the vascular introducer sheath, from the arterial puncture site. The procoagulant remains in place, effecting permanent hemostasis.

is inflated, the balloon assumes an elliptical shape with a significantly larger diameter (approximately 7 mm) and a relatively short length (approximately 3 mm). This configuration provides optimal temporary sealing of the arterial puncture from the luminal side by ensuring a large surface area of balloon in apposition to the puncture site, and at the same time minimizing obstruction to flow through the lumen of the vessel. On deflation, the moveable core wire can be advanced, thereby elongating the deflated balloon and ensuring a low profile for removal of the catheter. Finally, a lubricious polymeric sleeve can be advanced over the deflated balloon to further decrease the balloon profile and abolish any winging effects.

The procoagulant is a suspension comprised of 500 mg of bovine microfibrillar collagen (Avitene; Medchem Inc, Woburn, Massachusetts) and 20,000 U of bovine thrombin (Jones Medical Inc, St. Louis, Missouri) reconstituted in 10 ml of phosphate buffered saline for optimal viscosity, tonicity, and pH.

After completion of the cardiac catheterization procedure, the balloon catheter sealing device was advanced through the hemostasis valve of the femoral artery sheath. The balloon was inflated (approximately 2 atm) using isotonic saline and retracted to the puncture site. Optimal positioning of the balloon was ensured by noting an abrupt cessation of bleeding from the puncture site and resistance to further retraction of the catheter. Gentle traction was applied to maintain the balloon in this position. The procoagulant solution (5 to 10 ml) was then injected through the sidearm of the hemostasis sheath. The sheath was slowly withdrawn during injection of the procoagulant to fill the tract created by the sheath.

Immediately after injection of the procoagulant, the balloon was deflated, the moveable core wire advanced, the lubricious polymeric sleeve was positioned over the deflated balloon, and the entire device was then removed from the arterial access site (Figure 2). Manual pressure was then applied to the puncture

	Diagnostic Procedure	Interventional Procedure
Deployment time (min)	4.1 ± 1.7	5.4 ± 2.6
Compression time (min)	2.5 ± 0.9	6.0 ± 2.2
Time to hemostasis (min)	6.5 ± 2.1	11.4 ± 2.9
Time to ambulation (hr)	2.6 ± 0.5	16.3 ± 4.9
Device success rate	19/19 (100%)	5/5 (100%)

	Hemoglobin (g/dl)	Ankle-Brachial Index
Before deployment	14.8 ± 1.7	1.11 ± 0.14
After deployment	14.8 ± 1.4	1.16 ± 0.12
30-Day follow-up	13.7 ± 1.3	1.08 ± 0.12
p Value	<0.01*	<0.4*

*Thirty-day follow-up compared with before deployment measurements. No abnormalities were detected by Doppler ultrasound before or after sealing device deployment.

site. The puncture site was assessed by complete removal of manual pressure every 2 minutes for diagnostic procedures and every 5 minutes for interventional procedures until complete hemostasis was confirmed.

The time to hemostasis (minutes) was measured from initiation of sealing device deployment until complete cessation of bleeding in the absence of any type of external compression. The time to ambulation (hours) was measured from the end of the catheterization procedure until the patient was able to walk 3 to 5 steps independently without any resultant complications.

All patients were carefully observed for 24 hours after sealing device deployment or until discharge from the hospital if this occurred earlier. All patients were instructed to return for follow-up evaluation at 1 month (3 to 6 weeks). Patients were evaluated before device deployment, before discharge, and at 1 month with the following tests: clinical assessment of the femoral arterial puncture site (pulse strength rated on a scale of 0 to 4, hematoma diameter in centimeters, presence of a bruit or pulsatile mass, evidence of active bleeding or infection, and pain level on a scale of 0 to 10); assessment of distal pedal pulses (rated on a scale of 0 to 4); ankle-brachial systolic blood pressure index; Doppler ultrasound; basic laboratory blood tests (complete blood and platelet counts, international normalized ratio, activated clotting time, partial thromboplastin time); blood tests for disseminated intravascular coagulation (D-dimer, fibrinogen); and coagulation markers for thrombin activity or generation (thrombin-antithrombin-3 complex, prothrombin fragment 1 and 2). The coagulation tests were all performed at a central laboratory at the University of Munich by WS.

Statistical analysis: All group data are expressed as mean ± SD. The Student's *t* test or analysis of variance was used for comparing results in all patients before, after, and at 1-month follow-up. A *p* value <0.05 was considered significant.

RESULTS

In-hospital results: In-hospital results are listed in Table I. A total of 23 patients (age 61 ± 10 years, weight 77 ± 11 kg, 16 men) underwent deployment of 24 sealing devices (1 patient received 2 devices during separate invasive procedures on different days). The sealing device was successfully deployed in all 24 procedures. The procedures were 19 diagnostic and 5 interventional catheterizations. The introducer sheath

sizes were 5Fr to 8Fr (1 to 5Fr, 2 to 6Fr, 19 to 7Fr, and 2 to 8Fr). Systolic blood pressure immediately before device deployment was 147 ± 19 mm Hg. None of the diagnostic patients received heparin during the procedure. All interventional patients received at least 10,000 U of heparin (range 10,000 to 15,000), 500 mg of intravenous acetylsalicylic acid, and 250 mg of oral ticlopidine before the procedure. The predeployment activated clotting time (Hemotec, Medtronic Inc, Minneapolis, Minnesota) measured 126 ± 22 and 268 ± 60 seconds (range 213 to 364) in the diagnostic and interventional groups, respectively.

The mean time to hemostasis (including the time to deploy the device) was 6.5 ± 2.1 and 11.4 ± 2.9 minutes for the diagnostic and interventional procedures, respectively. The actual compression time was 2.5 ± 0.9 and 6.0 ± 2.2 minutes for the diagnostic and interventional procedures, respectively. Remarkably, no patient experienced even minor oozing from the arterial access site after initial hemostasis.

The mean time to ambulation (from the end of the antecedent invasive procedure) was 2.6 ± 0.5 and 16.3 ± 4.9 hours for the diagnostic and interventional procedures, respectively.

In 16 of 24 deployments (67%), patients did not experience any noticeable discomfort at the femoral puncture site. In 8 deployments there was temporary discomfort during procoagulant injection (3 were mild, 5 [21%] were moderate to severe). The discomfort subsided within minutes of completing the procoagulant injection.

There were no major in-hospital complications. No patient experienced a significant hematoma (6 cm) or required a blood transfusion. No patient underwent vascular surgical repair of the femoral artery puncture site or ultrasound compression of a pseudoaneurysm. There was 1 transient vasovagal reaction that occurred immediately after a diagnostic procedure during sealing device deployment, which responded promptly to fluid infusion and intravenous atropine.

Follow-up results (1 month): All patients returned for 1-month follow-up evaluation. No major device-related complications were encountered. Clinical evaluation of the femoral arterial puncture site and distal pedal pulses revealed normal healing and no significant changes compared with baseline evaluation performed before device deployment. The before- and after-deployment hemoglobin measurements, ankle-

Test NR Units	Platelet Count 130–400 × 10 ³ /mm ³	D-dimer ≤400 µg/L	Fibrinogen 180–350 mg/dl	F1.2 0.44–1.1 nmol/L	TAT-3 1.0–4.1 µg/L
Before treatment (mean ± SD)	218.4 ± 52.3	221.3 ± 157.6	340.2 ± 82.0	1.34 ± 0.62	11.5 ± 15.8
Median	206	185	334.5	1.14	4
(range)	(155–352)	(40–760)	(133–542)	(0.66–3.21)	(2–60)
After treatment (mean ± SD)	213.8 ± 44.4	852.9 ± 757.5	326.0 ± 51.5	1.99 ± 1.51	20.7 ± 19.2
Median	205	515	326	1.69	12.5
(range)	(145–309)	(160–2,920)	(194–409)	(0.82–8.14)	(3–60)
30-Day follow-up (mean ± SD)	219.2 ± 67.5	914.8 ± 1,977.9	326.0 ± 114.0	1.46 ± 0.79	7.8 ± 15.2
Median	198	330	281	1.34	2
(range)	(129–430)	(40–8,760)	(213–692)	(0.68–4.19)	(2–60)

F1.2 = prothrombin fragment 1 + 2; TAT-3 = thrombin-antithrombin-3 complex.

brachial systolic blood pressure indexes, and Doppler ultrasound results are summarized in Table II. There was no significant change in the ankle-brachial systolic blood pressure index on follow-up. Although a statistically significant decrease in the hemoglobin measurement was noted at 1-month follow-up, this was clinically mild and likely because a number of the patients underwent additional interventional procedures or coronary bypass surgery in the intervening 1-month follow-up period. In 1 patient, surgical exploration of the puncture site was performed 1 week after sealing device deployment because of clinical and angiographic suspicion of a possible arteriovenous fistula. However, at the time of surgery no abnormality was identified, and the procedure was aborted. The initial percutaneous arterial puncture in this patient was thought to have been traumatic and possibly associated with a posterior arterial wall puncture with involvement of the adjacent femoral vein.

Coagulation parameters: To evaluate for possible systemic coagulation effects of the sealing device and procoagulant, a number of blood and serologic parameters were measured before and after device deployment and at 1-month follow-up (Table III). Several patients underwent coronary artery bypass surgery after the catheterization procedure, which may have further influenced results of these tests at 1-month follow-up.

DISCUSSION

Sealing the arterial puncture site immediately after diagnostic cardiac catheterization or percutaneous coronary intervention significantly improves patient comfort and may also reduce length of hospital stay and total procedural costs. Various sealing devices using different approaches are currently commercially available and are effective in the face of anticoagulants or abciximab.^{15–19} Compared with manual compression, a gain in time to hemostasis of 12 to 16 minutes can be achieved in patients undergoing diagnostic cardiac catheterization.²⁰ After coronary intervention, the gain in time between sheath removal and complete hemostasis is approximately 14 to 30 minutes.²⁰ Although some differences regarding minor local complications may exist, none of these sealing devices has been shown to reduce major local complications.²¹

The novel approach reported herein may mitigate many of the limitations associated with manual compression and other recently described arterial access site management techniques. The device is based on techniques that are familiar to most invasive cardiologists. The balloon catheter is simple to position in the luminal side of the arterial puncture through most of the commonly used vascular introducer sheaths and sizes (thereby avoiding any enlargement of the tissue tract or arterial puncture). The procoagulant suspension is composed of hemostatic agents that individually have been well characterized and approved for human use by the Food and Drug Administration in other surgical applications to achieve effective hemostasis. The combination of thrombin (which induces platelet activation and promotes coagulation) and collagen (which is known to induce platelet adhesion and activation^{12,13}) may be optimal to achieve rapid hemostasis at the arterial puncture site. The suspension incorporating both of these hemostatic agents is designed to have a suitable viscosity for injecting through the sidearm of most vascular introducer sheaths, yet have a consistency that would likely maintain the procoagulant material at the desired location in the periarterial space at the puncture site. These aspects of the device may partially explain the remarkable absence of any delayed oozing from the arterial access site that frequently plagues other sealing approaches, causing significant nursing and patient concerns.

The major goal of this initial study was to assess the safety and efficacy of this new approach to vascular sealing. As a result, the measured times to hemostasis and ambulation may have been artificially prolonged, particularly in the patients undergoing interventional procedures. As noted in the Methods section, the compression times were evaluated at 5-minute intervals. Shorter assessment intervals may have revealed that the time to hemostasis was even shorter than that seen in this study. Similarly, there was no emphasis placed on ambulating patients soon after the procedure.

The most important concern related to the use of this and other devices using hemostatic agents is the risk of inadvertent intravascular administration, which could lead to extensive intraarterial thrombosis with

resultant limb ischemia or infarction. However, the design and deployment technique of this device makes the possibility of intravascular injection highly unlikely, as evidenced by the fact that there was no clinical, Doppler ultrasonographic, angiographic, serologic, or other evidence suggesting intraarterial injection or leakage of the procoagulant in the extensive preclinical studies that we have performed.¹⁴ In the present study, in light of the patients' clinical status and recent invasive catheterization procedure, there was no evidence of disseminated intravascular coagulation or inappropriately elevated levels of thrombin activity or generation (personal communication, W. Schramm). The encouraging results of the first human study with this novel vascular sealing device are currently being confirmed by an ongoing multicenter randomized trial.

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