Clin. Cardiol. 20, 981–992 (1997)

Review

Rapid Hemostasis of Arterial Puncture Sites with Collagen in Patients Undergoing Diagnostic and Interventional Cardiac Catheterization

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Summary: Despite the continuous reduction of sheath sizes in diagnostic and interventional cardiac catheterizations and the discontinuation of coumadin use after coronary stent implantation, a challenging role remains for hemostatic devices in the sealing femoral puncture sites. Since the introduction of the vascular hemostatic device (VHD) in 1991 and the hemostatic puncture closing device (HPCD) in 1992, numerous studies investigating these devices have been published. The deployment success rates reported in 2,292 patients for VHD is 97%, ranging from 88 to 100%. For HPCD, the mean deployment success rate resulting from 622 published patients leads to an identical result of 97%, ranging between 91 and 100%. For time to hemostasis, data have been analyzed according to the four different clinical situations, depending on level of anticoagulation (none or full) and the time of sheath removal (immediate or delayed). In randomized studies, when compared with the manual control groups, both devices revealed a statistically significant reduction in time to hemostasis: 12 to 16 minutes less for diagnostic catheterization and 14 to 30 minutes less for PTCA. As for minor local complications, no clinically relevant differences seem to exist. None of these devices has been proven to reduce major local complications. Prospective trials addressing early mobilization after percutaneous transluminal coronary angioplasty and the cost effectiveness of arterial closure devices in defined subgroups are warranted.

Key words: collagen, hemostasis, complication, cardiac catheterization, percutaneous transluminal coronary angioplasty

Introduction

Despite the continuous reduction of sheath sizes in diagnostic and interventional cardiac catheterizations and the discontinuation of coumadin use after coronary stent implantation, a challenging role for hemostatic devices in sealing femoral puncture sites remains: patients undergoing diagnostic coronary angiography may be ambulated almost immediately and discharged many hours earlier than currently practiced in most centers utilizing a supine restriction period of 6 h after diagnostic catheterization.[1] On the other hand, patients undergoing percutaneous transluminal coronary angioplasty (PTCA) by the femoral approach (which is the access used far more frequently than the brachial or radial approach[2]) are usually immobilized overnight, which may result in significant discomfort with increased back pain and need for analgesics.[3] In patients with low-risk procedures, when prolonged vascular access does not seem to be needed, sheath pulling immediately after PTCA increases patients' comfort (returning to their rooms without a sheath), decreases burden for the medical staff, and may reduce hospital costs by shortening the length of stay. Hemostatic devices may allow patients to walk 2 to 3 h after the end of the procedure and hence further increase their comfort. In addition, even with the current stent protocols using aspirin and ticlopidine, major local bleeding complications may still occur in 1% [STRESS III (Stent Restenosis Study), ISAR (Intracoronary Stenting Antithrombotic Regimen)], up to 2.2% [STARS (Stent Anticoagulation Regimen Study)], and 2.4% [FANTASTIC (Full Anticoagulation versus Ticlopidine plus Aspirin after Stent Implantation)].[4–7] Furthermore, glycoprotein IIb/IIIa inhibitors are increasingly used in both high- and low-risk patients: although the increased rate of bleeding complications in the EPIC study (Evaluation of c7E3 for the Prevention of Ischemic Complications) could be significantly reduced by decreasing the concomitant heparin dosage,[8] the EPILOG (Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIb/IIIa Receptor Blocker) and RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) trials still revealed a rate of major bleeding of 1.8 and 2.5%, respectively, in the patients treated with glycoprotein IIb/IIIa inhibitors, and even of 2.3 to 3.1% in the placebo groups.[8, 9] The use of low molecular weight heparin in patients at high risk for stent thrombosis may also be associated with a higher bleeding risk.[10]

Since there has been no published overview summarizing and analyzing the results for collagen devices, it is the purpose of this paper to review the data and to provide a differentiated analysis of success and local complication rates for

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Received: May 1, 1997
Accepted with revision: August 21, 1997

patients undergoing diagnostic or interventional cardiac catheterizations.

Characterization of Protocols and Patients Enrolled

To analyze the studies, it is important to differentiate between the protocols investigated. With regard to hemostasis, four different clinical situations may be encountered: (1) immediate sheath pulling after diagnostic catheterization is usually related to smaller sheath sizes and to no or a low level of anticoagulation; (2) after PTCA (or other coronary interventions), which are usually performed using larger catheters, sheaths may have been pulled with delay and without continued anticoagulation at a time when little or no anticoagulation is effective; (3) on the other hand, delayed sheath-pulling in patients under continued full anticoagulation (prolonged heparin administration or on coumadin according to previous stent protocols) must be strictly discerned; and (4) sheath pulling immediately after PTCA is, of course, always performed under full anticoagulation. Unfortunately, many of the published studies did not differentiate between these clinical settings and thus reported a mixture of overall results.

The exclusion criteria used in most of the studies were quite homogeneous: inadvertent penetration of the dorsal arterial wall with the puncture needle, previous application of collagen sealing of the femoral access site, known allergy to collagen, clinical signs of or known peripheral artery disease, acute myocardial infarction, status post thrombolytic therapy, known coagulation defects or known platelet dysfunction, severe and uncontrolled arterial hypertension (systolic > 220 mmHg or diastolic > 120 mmHg), preexisting hematoma or hematoma developed during the procedure, or patients with a venous femoral sheath.

Definition of Hemostasis

Basically, two parameters of measuring the success of hemostasis have been reported: the mean value of the times until complete hemostasis occurred in each individual patient (time to hemostasis) and the percentage of patients showing complete hemostasis after a specified time interval (hemostasis success rate). Although theoretically both parameters can be measured simultaneously, most of the studies reported only either one parameter or incomplete data.

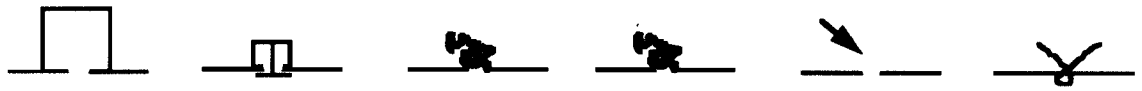
Time to Hemostasis

Time to hemostasis is defined as the time elapsed from initial compression at removal of the sheath until the completion of compression. The first time at which no bleeding occurs is taken as the time to hemostasis in a particular patient. However, the measurement of time to hemostasis is not standardized: results for time to hemostasis intrinsically depend on the time interval to the first and between the subsequent checks for bleeding; using a minimum time resolution of, for example, 15 min, one cannot expect to find a time to hemostasis of < 15 min. Table I summarizes the time intervals be-

TABLE I Published time intervals between sheath removal and checking for hemostatsis in collagen studies for determination of time to hemostasis. Some studies did not clearly define all time intervals ("?")

First author (reference)	Patients/groups	First check interval (min)	Subsequent intervals (min)
VHD			
Sanborn (11)	Collagen (diagn + PTCA)	1–2	Oozing: 2–5 Brisk: 5–10
	Control-diagn	10	?
	Control-PTCA	15	?
Ernst (12)	Collagen (diagn + PTCA)	2–3	?
Schräder (13)	Collagen (diagn + PTCA)	3–5	?
	Control (diagn + PTCA)	15	10
Foran (14)	Collagen (diagn+ PTCA)	3	?
Bartorelli (15)	Collagen (PTCA)	1	1
von Hoch (16)	Collagen (PTCA)	2	?
	Control (PTCA)	?	?
Silber (17)	Collagen (PTCA)	2	5
	Control (PTCA)	2	5
HPCD			
Kussmaul (18)	Collagen (diagn + PTCA)	?	?
	Control (diagn + PTCA)	15	10
de Swart (19)	Collagen (diagn + PTCA)	0.5	1, 2, 10
Murrary (20)	Collagen (diagn + PTCA)	5	10

Abbreviations: diagn = diagnostic, PTCA = percutaneous transluminal coronary angioplasty, VHD = vascular hemostatic device, HPCD = hemostatic puncture closing device.



Technique	Plug	Sandwich	Gel	Gel	Heat	Mechanic
Material	Collagen	Collagen + anchor	Thrombin/ collagen	Thrombin/ fibrin	Radio-frequency	Suture
Name	VasoSeal® (VHD)	Angio-Seal™ (HPCD)	Duet™ (GVSD)	BioSeal	?	Prostar™ TechStar™
Company	Datascope	Sherwood/ Quinton	Vascular Solutions	Global Therapeutics	Scimed	Perclose

FIG. 1 Devices used for sealing arterial puncture sites. VHD=vascular hemostatic device, HPCD = hemostatic puncture closing device, GVSD = Gershony vascular hemostatic device.

tween sheath removal and the first check as well as the subsequent time intervals used in studies determining time to hemostasis with collagen devices. As one can see, time intervals between 30 s and 15 min have been used for the first check interval, and between 1 min and 10 min for the subsequent intervals. Furthermore, not all studies clearly defined the time intervals for all the groups investigated; in some studies, even the time intervals within the same study varied. The choice of the time interval between the bleeding checks is an ambiguous decision: too short intervals may not give sufficient time for thrombus formation and may artificially increase—particularly in the manual control groups—the time to hemostasis.

In some studies, after deployment of a hemostatic device, all patients automatically received a vascular C-clamp[21] or an air cushion device.[22] Therefore, the determination of time to hemostasis was not possible in these studies.

Hemostasis Success Rate

This parameter reveals the percentage of patients showing complete hemostasis at a specified point of time. The shorter the time interval defined, the lower the success rate. Thus, in addition to sheath size and level of anticoagulation, when comparing the results for hemostasis success rates one must consider possible differences of the time points at which the success rate was measured. The time intervals for determination of hemostasis success rates range from 0 s (immediate hemostasis[19, 23, 24] to 2 to 5 min[12, 13, 17, 18, 22, 25, 26] and even up to 1 h.[21]

Vascular Complications

In this analysis, the definitions of major and minor vascular complications were used according to the U.S. multicenter trial.[11] The following complications were classified as major: thrombosis or loss of distal pulses, large pseudoaneurysm or atrioventricular (AV) fistula, and bleeding with need for transfusion or vascular surgery. Bleeding from puncture site that did not need transfusion and/or vascular surgery, as well as a small pseudoaneurysm treated medically, were classified as a minor complications.

Hemostatic Devices

Sandbags do not reduce vascular complications and even increase patient discomfort.[27] Mechanical devices such as C-clamps, stasis buttons, or air cushions were used as a replacement for manual compression, but upon physical examination did not clearly show a reduction in hematoma formation.[28, 29] Recent data suggest a reduction in ultrasound-detected AV fistulae and pseudoaneurysms with the C-clamp.[30] Mechanical devices cannot, of course, reduce the time to hemostasis and therefore cannot decrease the minimum time required for bed rest.

Hemostatic devices for rapid closure of arterial puncture sites may be classified according to their mechanisms, as illustrated in Figure 1. The vast majority of clinical experience has been gained using bovine collagen devices: the prototype was the vascular hemostatic device (VHD) (Fig. 2, VasoSeal®, Datascope Corp., Montvale, N.J.), a pure collagen plug device, followed by the hemostatic puncture closing device (HPCD) (Fig. 3, Angio-Seal™, originally developed by the

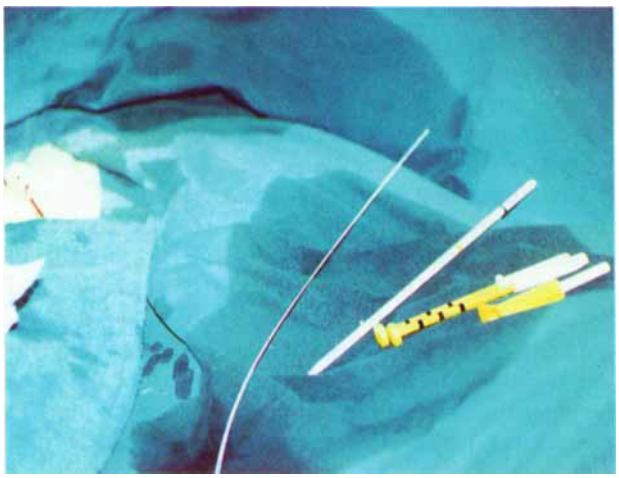


FIG. 2 The VHD (vascular hemostatic device, VasoSeal®) comprises a blunt-tipped 11-F dilator (center) which is inserted using the short guide wire, a short 11.5-F sheath (right), and two 90 mg collagen cartridges (between the above).

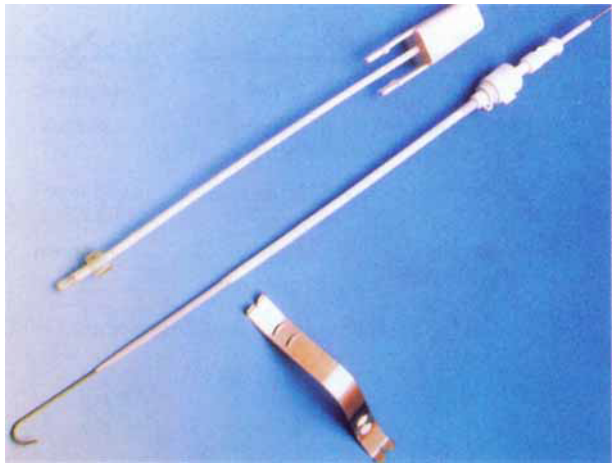


FIG. 3 The HPCD (hemostatic puncture closing device, Angio-Seal™) consists of a short guide wire, a dilator with 2 lumina, an 8-F sheath (mounted together, center), the "carrier" device (containing the anchor, the collagen, and the suture, above), and a tamper (below).

Kensey Nash Corporation, Exton, Pa.; it is now a trademark of Quinton Instrument Company, Bothell, Wash., within the USA, and of Sherwood Davis & Geck, St. Louis, Mo., outside the USA). In addition to the collagen, the HPCD applies an intra-arterial anchor. Both devices are discussed in detail below.

Another approach is the installation of a fibrin sealant via the arterial sheath. Fibrin sealant is a well-known tissue adhesive which combines fibrinogen (from human plasma) and (bovine) thrombin to form fibrin. The first encouraging results were obtained in animals and in 20 patients.[31, 32] The widespread application of fibrin may, however, be limited by the need for use of human plasma products. Therefore, the Gershony Vascular Sealing Device (GVSD) (Duet™, Vascular Solutions, Inc., Minneapolis, Minn.), using a mixture of bovine thrombin and collagen, may be more promising.[33] A different way of inducing hemostasis is the application of low-energy radiofrequency (30–35 W) via a guide wire through subcutaneous tissue to the periarterial wall.[34] First clinical results in 55 patients have been reported; the success rate seems to be related to the level of anticoagulation.[34]

The clinical findings using suture devices (Perclose, Inc.) are controversial. The Prostar™ device uses four needles (two sutures); the Techstar™ device uses two needles (one suture). After predilation of the subcutaneous tissue (requiring a 21-F tissue track), the suture-containing device is advanced into the artery, the needles are retracted, and knots are tied against the arterial wall, facilitated by a knot-pushing tool.[35] Whereas preliminary results with the Prostar device were encouraging, the relatively high rate of local vascular complications in the U.S. multicenter trial make further analysis necessary.[35, 36] Modifications of the Prostar Plus and Techstar devices seem to provide more reliable results;[37, 38] the use of both devices in a single center with high volume experience was, however, associated with a need for vascular repair in 2.1% of the patients undergoing PTCA.[39] Furthermore, the deployment success rate of 89.6% (786/877 patients) even with the 6F-Techstar device appears relatively low.[40]

Comparing the Vascular Hemostatic and Hemostatic Puncture Closing Devices

The basis of VHD and HPCD is collagen. Purified bovine collagen has been used in vascular, abdominal and dental surgical procedures since late in 1960 as an adjunct to hemostasis when control of bleeding by ligature or other conventional methods was insufficient.[41–43] The biodegradable collagen plug induces platelet activation and aggregation, releasing coagulation factors and resulting in the formation of fibrin and the subsequent generation of a thrombus.[44] It is assumed that anticoagulation with heparin or even antiaggregation with aspirin do not affect hemostasis induced by collagen.[12, 45] Collagen is ultimately degraded and resorbed by granulocytes and macrophages. These cells, releasing their collagenase enzymes, invade the plug and selectively digest the collagen as a function of the physical properties of the different collagens.[46] The immunogenicity of collagen has been a subject of debate, focusing in particular on injectable collagen, which is used to correct dermal defects such as acne or wrinkles. The reports of a possible link of collagen to autoimmune disease have implicated only injectable collagen, which is quite different in structure and the degree of cross-linking from the collagen sponge used in VHD and HPCD. Antigenicity of purified collagen is considerably reduced and, although allergies to collagen have been described,[47] allergic reactions to VHD have not been a clinical problem.[11–13]

Device Description and Deployment

The VHD consists of a purified collagen plug that induces the formation of a hemostatic cap directly over the arterial puncture site when inserted adjacent to the arterial wall. The method of its deployment is described in detail elsewhere.[11, 12] In brief, VHD deploys a collagen plug onto the external arterial wall after dilation of the skin and subcutaneous tissue to 11.5 F. It comprises four parts: a blunt-tipped 11-F dilator, one of seven differently sized 11.5-F sheaths selected by length using a preprocedure needle depth measurement technique, and two 90 mg collagen cartridges. When the sheath is to be pulled, a short guide wire is inserted and the existing sheath is removed while complete hemostasis is maintained with manual compression. Then the blunt-tipped 11-F dilator is inserted over the guide wire just down to the site of the arterial puncture. Guidance is obtained by feeling the resistance of the dilator against the outer surface of the artery as well as by the marker on the dilator. The 11.5-F sheath is then advanced over the dilator down to the arterial surface. While still holding pressure, the dilator and the guide wire are removed and the collagen cartridge deployed with a "push and pull" movement. We saw in a previous study that one collagen plug is as effective as two, but is better tolerated.[25, 48]

The HPCD provides a mechanical block of the arterial puncture site with an anchor from inside the artery, guiding

and holding the collagen in the tract. It consists of four components within a single delivery device ("carrier") requiring an 8-F sheath: anchor, collagen plug, connecting suture, and a tamper. All three components deployed into the patient (anchor, suture, and collagen) are completely resorbable; the anchor and the suture are made from polyglycolic and polylactic acids. The small plug contains only about 14 mg collagen. The technique of its deployment has been described in detail elsewhere.[18,19] In brief, a short guide wire is inserted and the existing sheath is removed while hemostasis is maintained with manual compression. First, the location of the end of the 8-F sheath within the artery is determined by inserting a modified dilator with two lumina: one (distal) for the guide wire and one (proximal) at the end of the 8-F sheath. The location of the end of the 8-F sheath is determined by the presence of blood flow through the modified dilator. Our preferred location of the sheath is ca. 1 cm further down the puncture site inside the artery lumen. The dilator is then removed and the carrier device is introduced into the 8-F sheath. The anchor is secured against the intraluminal arterial wall (we check three times at different angles) and the collagen plug is deployed on the outer arterial wall. A tamper is pushed downward to compress the collagen against the outer arterial wall ("sandwich technique"). Finally, a spring is attached between the tamper and a metal tag fixed to the positioning suture, thus applying continuous pressure on the tamper.[24] Although the deployment technique may sound complicated, it usually takes < 60 s to deploy the device.

The material used for the intra-arterial anchor of the HPCD is a 50:50 D,L polylactic-coglycolic acid copolymer and well established in medical use. It has a safe history, for it is widely used in sutures, bioresorbable meshes, and sustained release drug delivery systems. Some concern about the concept of inserting a foreign body (although resorbable) into the lumen of the artery has been expressed. After initial experience in animals,[49] ultrasound studies in patients have shown that HPCD caused no more changes in flow pattern than those observed in the control group with manual compression.[19,50] Therefore, the described changes of flow pattern after intra-arterial anchoring are related to the puncture procedure itself rather than to the hemostatic device.[19,50] In the majority of patients, the anchor is absorbed within 4 weeks;[50] after 2 months, complete absorption of the device was documented by ultrasound in all patients.[23] U.S. and European single and multicenter trials have established the safety of the concept of intra-arterial anchoring.[18,19,51]

Published Data Regarding Vascular Hemostatic and Hemostatic Puncture Closing Devices

Deployment Success Rates

Table II lists the results reported for a successful deployment of either VHD or HPCD: In 2292 patients reported, the deployment success rate for VHD is 97%, ranging from 88

TABLE II Deployment success rates of collagen devices

First author (reference)	No. of patients receiving device	No. of diagnostic patients	No. of PTCA patients	Deployment success rate (%)
VHD				
Sanborn (11)	246	90	156	98
Ernst (12)	252	105	140	98
Schräder (13)	50	30	20	100
Slaughter (26)	51	—	51	98
Foran (14)	63	46	17	91
Bartorelli (15)	100	—	100	100
Gibbs (52)	10	—	10	100
v Hoch (16)	154	—	154	88
Webb (21)	32	—	32	100
Kühn (53)	600	600	—	98
Silber (25)	660	660	—	98
Silber (17)	74	—	74	100
Total	2292			97
HPCD				
Kussmaul (23)	68	—	68	93
de Swart (19)	20	4	16	95
Aker (51)	30	26	4	91
Kussmaul (18)	218	168	46	96
Chevalier (54)	52	?	?	98
Blengino (55)	29	—	29	93
Silber (56)	65	65	—	100
Silber (24)	140	—	140	100
Total	622			97

Abbreviations as in Table I.

to 100%. For HPCD, the mean deployment success rate resulting from the 622 published patients leads to an identical result of 97%, ranging between 91 and 100%.

Time to Hemostasis

The published data on time to hemostasis for VHD and HPCD in patients undergoing diagnostic cardiac catheterization with no systemic or little administration of heparin is listed in Table III. The mean values for time to hemostasis vary between 1.7 and 4.3 min. In randomized studies, both devices revealed statistically significant reductions of time to hemostasis of about 12 to 16 min less than in the manual control groups.

In patients undergoing PTCA, the level of anticoagulation at the time of sheath removal was reported by most but not all groups (Table III). For VHD, a statistically significant reduction in time to hemostasis has been shown for immediate and for delayed sheath removal without prolonged anticoagulation (Table III). The one study using VHD in patients with delayed sheath removal and prolonged anticoagulation had no control group.[15] For HPCD, a statistically significant reduction in time to hemostasis has been shown for immediate and for delayed sheath removal with prolonged anticoagulation (Table III). For both devices, the average gain in time to hemostasis was approximately 14 to 30 min and therefore somewhat more than the gain in diagnostic patients. A gain in time to hemostasis for immediate sheath removal cannot be calculated, since there is no real control group for immediate sheath removal and manual compression.

The results of reports comprising a mixture of diagnostic and therapeutic interventions also showed an overall statistically significant reduction in time to hemostasis for VHD and HPCD (Table III). Not all authors, however, revealed data on the level of anticoagulation at the time of sheath removal (Table III).

Time to Ambulation

One of the primary goals using hemostatic devices is enabling patients to walk earlier. In most studies, however, early ambulation was not an end point, therefore the data of time to ambulation cannot be used for this purpose.[11, 18] To analyze the reported time to ambulation, it is important to know the

TABLE III Time to hemostasis using collagen devices. Differences can be attributed to different study designs regarding time of sheath removal and levels of anticoagulation

First author (reference)	No. of patients receiving device	ACT(s)/PTT(s)/INR at sheath removal and collagen application	Time to hemostasis (min)	
			Collagen group	Control group
Diagnostic patients				
Sanborn (11)	90 (VHD)	PTT = 35.6 ± 13.8	4.1 ± 2.8[a]	17.6 ± 9.2
Ernst (12)	105 (VHD)	—	4.3 ± 2.8 (0.5–20)	—
Kussmaul (18)	168 (HPCD)	ACT = 166 ± 58	2.3 ± 16.7[a]	13.6 ± 11.0
Condon (57)	31 (HPCD)	—	1.7[a]	18.4
PTCA-delayed sheath removal without prolonged anticoagulation				
Sanborn (11)	71 (VHD)	PTT = 36.2 ± 16.9	4.3 ± 3.7[a]	33.6 ± 24.2
Silber (17)	74 (VHD)	PTT = 49.4 ± 31.0	3.0 ± 3.0[a] (2–15)	17.4 ± 7 (5–75)
PTCA-delayed sheath removal and prolonged anticoagulation				
Bartorelli (15)	100 VHD	INR = 3.2 ± 2	2.2 ± 2.1 (1–8)	—
Kussmaul (23)	68 (HPCD)	ACT = 220 ± 94	4.4 ± 8.9	—
Kussmaul (18)	46 (HPCD)	ACT = 213 ± 89	3.5 ± 8.5[a]	19.6 ± 126
PTCA-immediate sheath removal				
Sanborn (11)	85 (VHD)	PTT = 52.9 ± 50.9	7.6 ± 11.6[a]	33.6 ± 24.2
Slaughter (26)	51 (VHD)	ACT = 381 ± 152	5[a] (3–15)	27 (18–40)
von Hoch (16)	117 (VHD)	—	5[a] (4–6)	27 (20–32)
Ernst (12)	140 (VHD)	—	5.3 ± 7.6 (20–32)	—
Blengino (55)	29 (HPCD)	ACT = 274 ± 61	2 ± 6[a]	16 ± 5
Mixed patient groups				
Schräder (13)	50 (VHD)	—	4.3 ± 3.0[a] (2–15)	42.3 ± 18.9 (20–120)
de Swart (19)	20 (HPCD)	—	1.2 ± 2.1	—
Chevalier (54)	52 (HPCD)	—	2.3 ± 6.7[a]	29.3 ± 23.2
de Swart (58)	55 (HPCD)	ACT = 159 ± 129	1.2 ± 1.6[a]	12.9 ± 5.6
Murray (20)	95 (HPCD)	ACT = 141 ± 57	1.9 ± 5[a]	20.0 ± 9

[a] $p < 0.05$.

Abbreviations: ACT = activated clotting time, PTT = partial thromboplastin time, INR = International Normalized Ratio. Other abbreviations as in Table I.

time of sheath removal (Table IV). Therefore, with delayed sheath removal after PTCA, a time to ambulation of 2 to 3 days is not surprising.[15, 52] Unfortunately, not all publications revealed the time of sheath removal (Table IV).

For diagnostic cardiac catheterization, two studies addressed the primary end point of early ambulation: with immediate sheath removal, patients were successfully ambulated 30 min after the deployment of VHD[25] and even 20 min after HPCD.[56] For patients undergoing PTCA, no study specifically investigating early ambulation has been published. In PTCA studies, the shortest time intervals to ambulation were in the range of 6 to 7 h for VHD,[26, 53] and 8 h for HPCD.[18] In mixed patient populations, after diagnostic or therapeutic cardiac catheterization, attempts were made to ambulate patients within 2 h after the deployment of VHD[14] or starting at 4 h after HPCD.[19, 51]

Local Complications

Complications after manual compression: Vascular complications in patients undergoing diagnostic cardiac catheterizations occur in the order of 0.5%.[60] The incidence of major vascular complications (requiring blood transfusion or vascular surgery) in patients undergoing diagnostic cardiac catheterization has been reported to range from 0.35 to 5%.[61–65] While in earlier decades these incidences often included thrombosis and distal embolism, later studies reported lower vascular complication rates of <0.5%, reflecting improved equipment and extensive operator experience.[60, 66] With the use of 5F-catheters for outpatient coronary angiography, major and minor complications were less frequent than reported earlier.[66] In recent studies, major vascular complications (as defined above) did not occur in patients undergoing diagnostic cardiac catheterization.[11, 19, 26] Small hematomas are only scarcely reported; many centers do not report them and/or consider them unimportant.[2, 60] Kern *et al.* reported 8% (23/287) minor hematomas in outpatients undergoing 5F-catheterizations.[66]

Complications after collagen devices: The complication rates reported for collagen plugging are somewhat confusing, because several studies did not differentiate between diagnos-

TABLE IV Time to ambulation using collagen devices

First author (reference)	No. of patients receiving device	Time of sheath removal	Time to ambulation
Diagnostic patients			
VHD			
Sanborn (11)	90	?	13.3 ± 12.1 h
Silber (25)	660	Immediately	30 min
Silber (56)	65	Immediately	20 min
HPCD			
Kussmaul (18)	168	56 ± 171 min	4–12 h
Silber (56)	65	Immediately	20 min
PTCA patients			
VHD			
Bartorelli (15)	100	Next day	>3 days
Gibbs (52)	10	Immediately	>2 days
Sanborn (11)	85 (on heparin)	Immediately	16.1 ± 11.1 h
Sanborn (11)	71 (off heparin)	Delayed	23.0 ± 11.1 h
Slaughter (26)	51	Immediately	8.5 (7–17) h
Camenzind (22)	62	Immediately	>12 h
Nagtegaal (59)	80	Immediately	9 ± 5 h
Kühn (53)	600	Immediately	6–12 h
HPCD			
Blengino (55)	29	?	15.8 ± 3.3 h
Kussmaul (18)	46	465 ± 523 min	8 h
Mixed patient groups			
VHD			
Ernst (12)	105 Diagn + 140 PTCA	Immediately	8.3 (1–24) h
Schräder (13)	30 Diagn + 20 PTCA	Immediately	6.4 ± 2.2 (4–12) h
Foran (14)	46 Diagn + 17 PTCA	Immed./delayed	"within 2 h or 1 h"
HPCD			
Aker (51)	26 Diagn + 4 PTCA	?	16.5 (4–57) h
Chevalier (54)	52	?	10.8 ± 7 h
de Swart (19)	4 Diagn + 16 PTCA	Immediately	6.7 ± 3.5 (4–18) h

Abbreviations as in Table I.

tic and interventional procedures and because various classifications of complications with different methods of measurement were used: in the European VHD multicenter trial, only the overall complications were reported for the 105 patients receiving the collagen plug after diagnostic procedure and for the 140 patients after interventional procedure, despite significant differences in the doses of heparin (5715 ± 4615 U vs. 15378 ± 3025 U). Activated clotting times or partial thromboplastin times were not reported.[12]

For VHD, some authors found a significant reduction in local complications,[13, 59] whereas other findings were nonconclusive.[11] In contrast, some reported an increased incidence of only minor[26] or even major complications[16] and therefore described collagen plugging of arterial puncture sites with VHD as a "deep disappointment."[67]

In these trials, however, the collagen groups were not compared with the control groups under identical conditions: in the collagen groups the sheaths were pulled immediately, whereas in the control groups the sheaths were pulled several hours later[13, 22, 59, 68] or even the next day.[14, 22] Because the sheath-dwell time represents one of the risk factors for local complications,[26, 69] this parameter should be kept constant in both groups to evaluate the possible influence of the collagen plug on local complications. We therefore performed a prospective, randomized trial with both groups having identical sheath-dwell times.[17] According to the classification of major and minor complications suggested by the U.S. multicenter trial,[11] one major complication needing vascular surgery occurred in the collagen group and none in the control group. When comparing minor complications in both groups, no statistical difference was found for the development of any hematoma. Significantly more patients assigned to collagen (4%) developed a large hematoma than patients assigned to conventional sheath pulling (0%).[17]

Tables V and VI list the published reports on local complications using VHD or HPCD in detail.

TABLE V Detailed analysis of studies reporting minor or major complications using the vascular hemostatic device (VHD)

	Minor complications				Major complications			
First author (reference)	Device group	%	Control group	%	Device group	%	Control group	%
Diagnostic patients								
Sanborn (11)	2/90	2.2	1/75	1.3	0/90	0	0/75	0
Silber (56)	2/65	3.1	—	—	0/65	0	—	—
Kadel (70)	—	—	—	—	4/521	0.8	0	0
Total diagnostic	4/155	2.6	1/75	1.3	4/676	0.6	0/75	0
PTCA patients								
Sanborn (11)	7/156	4.4	4/134	3	2/156	1.3	1/134	0.7
Slaughter (26)	4/51	7.8	0/50	0	0/51	0	0/50	0
Foran (14)	0/17	0	—	—	1/17	5.8	—	—
Stiel (71)	0/100	0	—	—	2/100	2	—	—
Camenzind (22)	4/62	6	0/62	0	6/62	10	4/62	7
Legrand (68)	10/120	8	4/120	3	3/120	2.5	0/120	0
Nagtegaal (59)	5/80	6.3	9/100	9	1/80	1.3	4/100	4
Silber (17)	4/74	5.4	3/76	3.9	1/74	1.4	0/76	0
Bartorelli (15)	2/100	2	—	—	2/100	2	—	—
Gibbs (52)	0/10	0	—	—	1/10	10	—	—
von Hoch (16)	20/154	13	17/155	11	21/154	13.6	5/155	3.2
Kiemeneij (70)	2/18	1.1	3/17	1.8	1/18	5.5	0/17	0
Webb (21)	3/32	0.9	—	—	1/32	0.3	—	—
Kadel (70)	—	—	—	—	7/499	1.4	—	—
Kühn (53)	65/600	10.8	—	—	61/600	10.2	—	—
Total PTCA	126/1574	8.0	40/714	5.6	110/2073	5.3	14/714	2.0
Mixed patient groups								
Ernst (12)	1/252	0.4	—	—	2/252	0.8	—	0
Schräder (13)	0/50	0	6/50	12	0/50	0	0/50	0
Carere (73)	9/159	5.7	—	—	2/159	1.3	—	—
Total mixed patients	10/461	2.2	6/50	12	4/461	0.9	0/50	0
All patients	140/2192	6.4	47/839	5.6	118/3210	3.7	14/839	1.7

Abbreviations as in Table I.

TABLE VI Detailed analysis of studies reporting minor or major complications using the hemostatic puncture closing device (HPCD)

First author (reference)	Minor complications				Major complications			
	Device group	%	Control group	%	Device group	%	Control group	%
Diagnostic patients								
Kussmaul (18)	9/168	5.3	17/152	11.2	6/168	3.6	4/152	2.6
Condon (57)	1/31	3.2	1/18	5.6	0/31	0	0/18	0
Silber (56)	0/65	0	—	—	0/65	0	—	—
Total diagnostic	10/264	3.8	18/170	11	6/264	2.3	4/170	2.4
PTCA patients								
Kussmaul (23)	9/68	13	—	—	0/68	0	—	—
Kussmaul (18)	6/46	13	16/63	25	1/46	2	1/63	1.6
Silber (24)	0/140	0	—	—	0/140	0	—	—
Total PTCA patients	15/254	5.9	16/63	25	1/254	0.4	1/63	1.6
Mixed patient groups								
Aker (51)	2/29	7	—	—	0/29	0	—	—
Chevalier (54)	4/52	7	11/48	23	0/52	0	0/48	0
de Swart (58)	4/55	7.3	3/54	5.5	0./55	0	0/54	0
Murray (20)	6/95	6.3	2/92	2,1	1/95	1	1/92	1
Total mixed patients	16/231	6.9	16/194	8.2	1/231	0.4	1/194	0.5
All patients	41/749	5.5	50/427	11.7	8/749	1.1	6/427	1.4

Abbreviations as in Table I.

Although both devices carry the inherent risk of inadvertent intra-arterial collagen insertion, published reports on this device-related complication exist only for VHD. (Table VII).

Cost Effectiveness

Hemostatic closure devices are expensive and have to prove their cost effectiveness.

Effectiveness can be defined as hemostatic success. So far, no study has proven one hemostatic device to be clearly better than others. Therefore, differences between these devices may be related to different costs.

TABLE VII Reports on intra-arterial complications (insertions or protrusions) using the vascular hemostatic device (VHD)

First author (reference)	Number	%
PTCA patients		
Camenzind (22)	1/62	1.6
Kühn (53)	2/600	0.3
Sanborn (11)	1/71	1.4
Stiel (71)	2/100	2.0
von Hoch (16)	2/154	1.3
Mixed patient groups		
Carere (73)	2/159	1.3
Foran (14)	1/63	1.6
Kadel (70)	4/1020	0.4
Total	15/2229	0.7

Costs may be divided into procedural costs, hospital costs, and follow-up costs. *Procedural costs* reflect the price of the device plus the time for deployment (cathlab time, doctors' time spent for deployment). In our facilities, VHD has the lowest price, HPCD is in the middle range, and suture devices are the most expensive. The time for deployment of either VHD or HPCD is similar (< 1 min), whereas the suture devices usually take us 4 to 5 min. *Hospital costs:* in Germany, hospitals are paid by the day (length of stay). In diagnostic patients undergoing catheterization in the afternoon, all hemostatic devices may make an overnight stay unnecessary and therefore save the costs for 1 day. There is, however, a conflict of interest between health insurers and hospitals: saving overnight stay is important to the health insurers, but leads to a loss of income for the hospitals. In patients undergoing PTCA, usually 1 or 2 days may be saved, with the same conflicting interests as described for diagnostic procedures. In our study, the decision to discharge was left to the ward physicians. Nevertheless, patients with collagen sealing were discharged 1 day earlier than the control group.[17] This is in good agreement with a U.S. study that reported a significant decrease from 2.4 ± 0.98 days (control group, 56 patients) to 1.53 ± 0.8 days (collagen group, 47 patients).[74] *Follow-up costs* are predominantly defined by local vascular complications; these complications may lead to substantial costs, even higher than that of the catheterization itself.[1] Hemostatic devices should at least not increase the rate of local vascular complications or, even better, lead to a decrease of complications. There is, however, no clear evidence that hemostatic devices decrease the rate of local complications; some devices even show a tendency to increase local complications.

Future Aspects

The data suggest that mechanical forces play a more important role in sealing arterial puncture sites with collagen than previously anticipated.[12] The collagen itself may not be that important for devices using intra-arterial anchoring[56] and could perhaps be replaced by nonbiological, resorbable materials. Besides device changes (like 6F-devices for 6F-PTCAs or 4F-devices for 4F-diagnostics), it is important to fill the gaps of missing studies that have early ambulation as primary end point after PTCA. Newer antiplatelet protocols with ticlopidine pretreatment and/or the administration of IIb/IIIa inhibitors also need to be investigated. Furthermore, prospective trials addressing the cost effectiveness of arterial closure devices in defined subgroups of patients are warranted.

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