AUS DER KLINIK FÜR KARDIOLOGIE,
PNEUMOLOGIE UND ANGIOLOGIE
(DIREKTOR: UNIV.-PROF. DR. MED. M. KELM)
DER MEDIZINISCHEN FAKULTÄT DER
HEINRICH-HEINE UNIVERSITÄT DÜSSELDORF

Erhöhung der Patientensicherheit durch kontinuierliche Prozessoptimierung in der täglichen klinischen Routine

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Habilitationsschrift zur Erlangung der Venia legendi für das
Fach Innere Medizin an der Medizinischen Fakultät der
Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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aus
Bonn

Düsseldorf 2016

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II Einleitung

Qualitätsmanagement (QM) in der Medizin führt nicht nur zu einer Erhöhung der Qualität der Versorgung sondern auch zu einer Verbesserung der Patientensicherheit sowie zu einer Kostenreduktion im Gesundheitswesen.[1,2]

Ursprung des Qualitätsmanagements

QM und Risikomanagement (RM) werden schon seit Jahrtausenden eingesetzt - auch in der Medizin. Bereits vor etwa 4000 Jahren entwickelten Nomaden Behandlungskonzepte und dokumentierten diese mittels Hieroglyphen auf Steintafeln. Etwa 1700 v.Chr. wurden diese modifiziert und als „Codex Hammurabi“ auf einer Stein Stele verbindlich publiziert.[3] Neben Tarifen für Behandlungsverfahren wurden hier auch Regeln der Kostenübernahme (Behandlungskosten für Sklaven) sowie Informationen über Standards und Patientenrechte bekannt gegeben. Auch der Eid des Hippokrates (ca. 400 v. Chr.) hält die Berufsgruppe der Ärzte durch eine Festlegung von Normen zu qualifiziertem Handeln an.[4]

Qualitätssicherung – Qualitätskontrolle – Qualitätsmanagement

Zunächst wird in den 50er Jahren des letzten Jahrhunderts das Verfahren der Qualitätskontrolle eingeführt. Im Rahmen dieses Verfahrens werden Stichproben genommen und überprüft. Am Ende eines Prozesses wird das Ergebnis einer Arbeit im Sinne der Erfüllung vorgegebener Anforderungen untersucht, mit dem Ziel einer Verbesserung der Strukturen, um Funktion, Lieferzeit, Preis und Service von Produkten und Dienstleistungen zu optimieren.[5] In den 60er Jahren kommt es dann zu einer Weiterentwicklung im Sinne der Qualitätssicherung.[6] Nun werden prozessorientierte Veränderungen vorgenommen, die eine Verbesserung der Produktionsabläufe zum Ziel haben. In den 90er Jahren mündet dies schließlich im sogenannten QM, welches

kunden- und ergebnisorientiert unter Einbeziehung der Mitarbeiter und der Prozesse als Instrument zur Motivation dienen soll. Hierbei haben die Reflexion von Qualität und die Etablierung künftiger Qualitätsziele einen besonderen Stellenwert.[7] Dem QM wohnt das RM als ein integraler Bestandteil inne.

Total Quality Management – Lean Management

Eine Optimierung alleine von Technik und Material ist jedoch kein Garant für Spitzenleistungen, bedeutende Rolle für den Erfolg eines Unternehmens ist die Einstellung der beteiligten Menschen.[8] Neben dem technischen System ist auch das soziale System zu betrachten und die Beziehungen zwischen beiden zu analysieren.[9] Diese Erkenntnisse führen zur Entwicklung des Total Quality Managements (TQM), welches Qualität zum obersten Ziel macht und alle Mitarbeiter auf die maximale Zufriedenstellung der Kunden ausrichtet.[8] Parallel entsteht als weiterer Begriff das „Lean Management“. Es steht für das Streben nach bestmöglicher Qualität unter Vermeidung von Verschwendung, Fehlern und unnötigen Kosten.[10] Somit wird es im Hinblick auf Effizienz und Qualität als das momentan überlegene Entwicklungs- und Produktionssystem angesehen. Weltweiter Benchmark ist das „Toyota“-Produktionssystem.[10–12] Übertragungen von Methoden des „Toyota“-Produktionssystems auf andere Bereiche, unter anderem auf die Medizin sind zahlreich und mit Erfolg.[2,13–17] Ein direktes Übertragen des „Toyota“-Systems gelingt jedoch in der Medizin nicht in allen Teilaspekten. Eine Besonderheit des Gesundheitswesens ist, dass die Qualität maßgeblich von den Patienten mitbestimmt wird. Deren Anforderungen an die erbrachten Dienstleistungen hängen jedoch maßgeblich von Kommunikation, Kooperation und Interaktion ab.[18]

Risikomanagement – Clinical Risk Management – Healthcare Lean Management

Das RM ist integraler Bestandteil des QM,[13] insbesondere in der Medizin spielt jedoch der Aspekt einer Risikobeeinflussung eine sehr wichtige Rolle, da auch kleine Fehler fatale Konsequenzen haben können und häufig unter sehr hohem Zeit- und Erwartungsdruck gearbeitet wird. So hat sich das Spezialgebiet des Clinical Risk Management entwickelt (CRM),[19–23] welches im Sinne des TQM[24] integriert wurde und den Begriff des Healthcare Lean Managements (HLM) geprägt hat.[25]

Qualitätsmanagement im deutschen Gesundheitswesen

Im deutschen Gesundheitswesen werden Qualitätsmaßnahmen gesetzlich gefordert.[26] Hintergrund sind zunehmende Finanzierungsprobleme des bundesdeutschen Gesundheitswesens aufgrund steigender Kosten. Diese entstehen einerseits durch eine zunehmende Alterung der Bevölkerung und Einsatz moderner und somit teurer Technologien und Medikamente, andererseits durch ineffizienten Einsatz von Ressourcen und dem Auftreten von Fehlern.[1,27,28] Bei schlechterer Qualität entstehen sowohl höhere direkte Kosten (höhere Ausgaben) als auch höhere indirekte Kosten (schlechtere Produktivität, höhere Fehlerrate, unmotiviertes Personal).[6,29,30] Darüber hinaus entsteht bei schlechter Qualität mangelndes Vertrauen seitens der Patienten und eine geringere Zufriedenheit von Patienten und Personal.[31] Im Gegenzug führt eine Qualitätsverbesserung zu einer Kostenreduktion und Erhöhung der Zufriedenheit.[1,28] Aus diesen Erkenntnissen resultiert eine gesetzliche Verpflichtung, welche seit 2005 von Krankenhäusern in Deutschland alle zwei Jahre die Erstellung eines strukturierten Qualitätsberichtes verlangt.[26] Dieser soll einen Vergleich der Krankenhäuser und Fachabteilungen anhand vordefinierter, gesetzlich festgelegter Merkmale ermöglichen.

Werkzeuge zum Qualitätsmanagement

Das Führen und Steuern einer Organisation hinsichtlich der Qualität ihrer Leistungen und Produkte kann nach Deming über das Definieren von Zielen, Planung, Lenkung, Sicherung und Verbesserung erfolgen.[32] Das Grundprinzip lässt sich im sogenannten „Deming-Kreis“, auch PDCA-Zyklus genannt, darstellen (Abbildung 1).

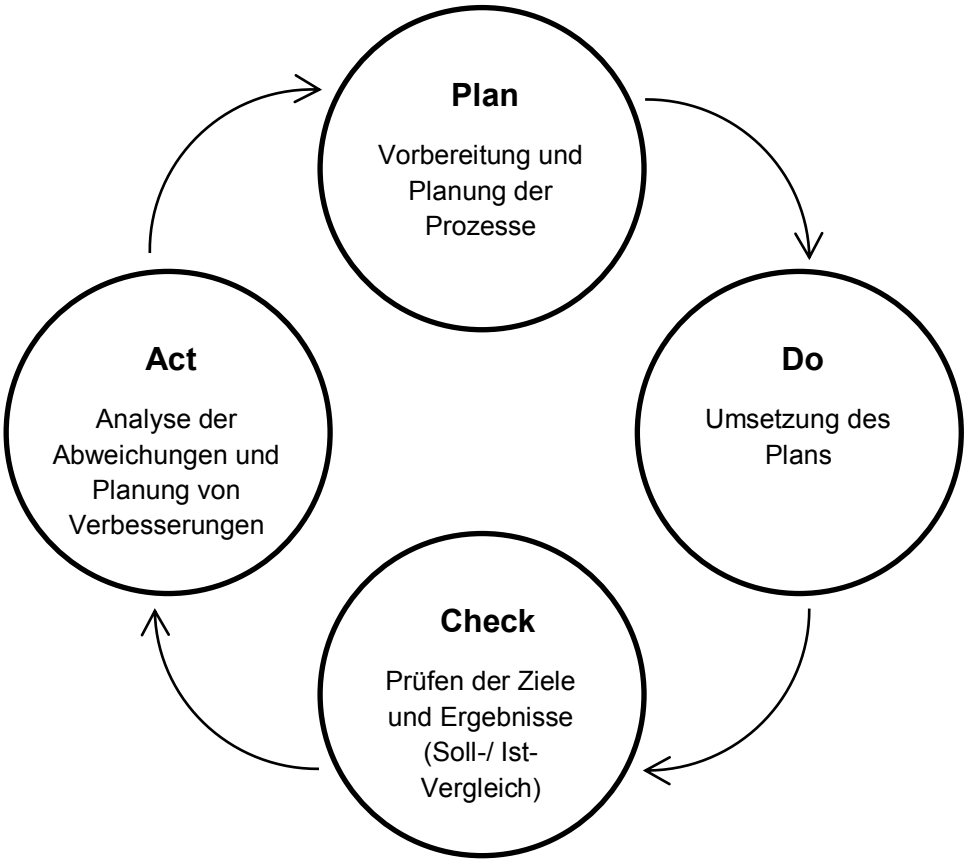

Abbildung 1: Deming-Kreis

Die Qualität wird hierbei im laufenden Prozess anhand von gesetzten Zielen geplant, gelenkt, gesichert und verbessert. Auch in der Medizin erfolgt das QM in Anlehnung an den PDCA-Zyklus.[33,34] Grundlage ist das Vier-Stufen-Konzept aus Erfassung - Optimierung - Überprüfung - Handeln, welches in der vorliegenden Arbeit ebenfalls angewendet wird.

III Fragestellung und Zielsetzung

Unter dem Aspekt des Qualitäts- und Risikomanagements werden die Prozessabläufe in einer universitären High-Volume-Kathetereinheit analysiert und anschließend die klinischen Abläufe anhand von Fehleranalysen angepasst, Risikokonstellationen herausgearbeitet, Prozessoptimierungsstrategien entwickelt und umgesetzt sowie anschließend differenziert überprüft.

Ziel der Arbeit ist eine kontinuierliche Prozessoptimierung unter Einbeziehung der zugrundeliegenden Strukturen, der verwendeten Techniken, der eingesetzten Materialien und der beteiligten Menschen im Sinne eines TQM zwecks Reduktion von Komplikationen und Qualitätsverbesserung im Zusammenhang mit durchgeführten Herzkatheteruntersuchungen.

IV Dargestellte Arbeiten

The frequency of vascular complications associated with the use of vascular closure devices varies by indication for cardiac catheterization

Stegemann E, Hoffmann R, Marso S, Stegemann B, Marx N, Lauer T

Clin Res Cardiol. 2011 Sep;100(9):789-95

Verschlusssysteme zum Einsatz nach arterieller Punktion wurden in den 90er Jahren entwickelt und fanden aufgrund hohen Komforts für Patienten und Untersucher eine rasche Verbreitung. Ihr Einsatz erfolgte zunächst nur in geplanten Untersuchungen, hier mit großem Erfolg und nachweislich verminderten Komplikationsraten. In dieser Arbeit werden die Komplikationsraten eines arteriellen Verschlusssystems bei Notfalleingriffen untersucht. Im Gegensatz zu den elektiven Untersuchungen zeigte sich eine erhöhte Komplikationsrate bei Patienten, welche im Rahmen eines akuten Herzinfarktes kathetert wurden.

Clin Res Cardiol
DOI 10.1007/s00392-011-0313-4

ORIGINAL PAPER

The frequency of vascular complications associated with the use of vascular closure devices varies by indication for cardiac catheterization

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Received: 16 November 2010 / Accepted: 25 March 2011

Abstract
Objective This study aimed at exploring access site-related vascular complication rates associated with the use of the vascular closure device (VCD) Angio-Seal™ in an unselected patient population undergoing elective as well as emergency coronary angiography or intervention.
Background The VCD Angio-Seal™ is widely used to achieve hemostasis after diagnostic and interventional cardiac procedures. There are only little data on the frequency of vascular complications after the use of the VCD Angio-Seal™ in patients in non-elective settings.
Method In-hospital vascular complications were prospectively assessed in 4,653 consecutive cardiac catheterization procedures, which included 2,772 elective diagnostic and 960 elective percutaneous coronary interventions (PCI), and 921 emergency cardiac catheterizations in patients with NSTEMI/STEMI. In 2,077 procedures manual compression (MC) and in 2,576 procedures VCD was applied. Complication rates for manual compression and VCD use were studied and multivariate analyses performed to disclose predictors for access site-related vascular complications.
Results Vascular complication rates in patients receiving MC to achieve hemostasis were similar to those receiving a VCD (MC 3.4% vs. VCD 3.2%, p = n.s.). Separate analysis of vascular complication rates for subgroups revealed a significant reduction in vascular complications for the PCI group using a VCD (MC 7.7% vs. VCD 3.2%, $p = 0.003$). In emergencies VCD use lead to a rise in vascular complications (MC 0.9% vs. VCD 6.3%, $p < 0.001$).
Conclusions In contrast to elective settings, the risk of access site-related vascular complications is significantly increased after application of the VCD Angio-Seal™ in patients undergoing emergency catheterizations for NSTEMI/STEMI compared with manual compression.

Keywords Vascular closure devices · Vascular complications · Coronary interventions · Acute coronary syndrome

Abbreviations

ACT	*A*ctivated *c*lotting *t*ime
BMI	*B*ody-*m*ass-*i*ndex
GPI	*G*lyco*p*rotein IIb/IIIa *i*nhibitor
MC	*M*anual *c*ompression
NSTEMI	*N*on-*ST*-*e*levation *m*yocardial *i*nfarction
PCI	*P*ercutaneous *c*oronary *i*ntervention
SOP	*S*tandard *o*perating *p*rocedure
STEMI	*ST*-*e*levation *m*yocardial *i*nfarction
TIMI	*T*hrombolysis *i*n *m*yocardial *i*nfarction
VCD	*V*ascular *c*losure *d*evice

Introduction

In the mid-1990s vascular closure devices (VCD) were developed as alternative to manual compression (MC) for arterial closure following cardiac catheterization procedures. The market launch of the Angio-Seal™ VCD

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Published online: 11 April 2011

(St. Jude Medical, Minnetonka, Minnesota) was in 1994; application in our clinic is carried out since April 1998. Numerous clinical studies have been performed in a variety of populations. These studies were predominantly performed in selected cohorts [1–8]. Several meta-analyses of these clinical trials demonstrated similar complication rates for VCD compared with MC [9–12]. However, there are only few prospectively collected data in the use of VCD in unselected patient groups. Recently, two large prospective registries of patients undergoing diagnostic and therapeutic cardiac catheterization revealed lower vascular complication rates after application of VCD considering all patient groups [13, 14]. In the first report, however, patients with cardiogenic shock or requiring intra-aortic balloon counter pulsation were excluded. Both registries included the application of different closure devices. Thus, there were four to six different VCD systems included. The aim of this study was to explore access site vascular complications associated with the use of the Angio-Seal^{TM} device in an unselected patient population, including all patients undergoing diagnostic or percutaneous coronary intervention (PCI) in elective and emergency settings.

Methods:

In this single-center study all transfemoral cardiac procedures performed from January to December 2006 were included. This relates to a total of 4,653 examinations. Patients with diagnostic catheterization received unfractionated heparin after sheath insertion at the discretion of the cardiologist performing the procedure. Anticoagulation after sheath insertion for PCI patients was obtained using unfractionated heparin with a target-activated clotting time (ACT) of 250–300, or 200–250 s if used in conjunction with glycoprotein IIb/IIIa inhibitors (GPI). Patients received GPI at the discretion of the treating physician according to usual protocol with abciximab or eptifibatide. Patients were given aspirin 100 mg daily and clopidogrel (300 or 600 mg as a loading dose followed by 75 mg daily) if patients underwent cardiac catheterization for suspected coronary artery disease and stents were placed or after NSTEMI/STEMI.

Access site management

The recommended fashion of sheath removal was VCD deployment in outpatient catheterization, elective PCI or catheterization for NSTEMI/STEMI. Thus, VCD use was predefined and consequently no randomization was performed. Sheath removal with MC took place in all inpatient diagnostic catheterizations and in patients with contraindications for VCD due to a common femoral artery angiogram. A femoral angiogram via the arterial sheath was performed in all cases prior to VCD deployment. Patients did not undergo arterial closure with a VCD if (1) the arteriotomy site was $\leq$2 cm proximal to the bifurcation of the common femoral artery, below the femoral bifurcation or above the inferior epigastric artery; (2) the common femoral artery had a vessel diameter $\leq$6 mm; (3) extensive calcification or plaque formation was present in the common femoral artery and; (4) extensive scar tissue was present at the access site. Closure was performed using exclusively the VCD Angio-Seal^{TM} during the complete study period. All operators had received training and had used the device in at least 50 cases before the study started.

VCD was applied immediately after the procedure. In patients in whom MC was used, the sheath was pulled when the ACT was $\leq$150 s. Ambulation was initiated 4 h after the VCD was placed and 6 h after MC. Effective anticoagulation or administration of GPI was followed by 12 h bandaging even if patients received a VCD.

Access site evaluation was carried out consistently in all patients. The assessment of the puncture site included an examination by a physician in all patients before and immediately after catheterization procedure, as well as after removal of the compression bandage. The examination before the catheterization procedure and after removal of the compression bandage was performed by the same person to ensure that changes were perceived. Any changes or abnormalities at the puncture site were reported to a vascular specialist resulting in vascular ultrasound and/or supplementary examinations such as computed scan tomography. The following complications were recorded: bleeding, defined as external blood loss requiring manual compression, oozing requiring light manual pressure, ecchymosis >5 cm in the soft tissue of the upper thigh, hematoma formation, retroperitoneal extension of hematoma, vessel obstruction or closure, pseudoaneurysm, arteriovenous fistula confirmed by either clinical examination, vascular ultrasonography or computed scan, infection of the puncture site, reduction in hemoglobin concentration, need for blood transfusion and need for surgery. Major vascular complications were defined as any of the following: need for surgery, infection requiring intravenous antibiotics or surgical lancing, retroperitoneal hemorrhage, bleeding requiring blood transfusion, pseudoaneurysm, hematoma associated with a decline in hemoglobin concentration by $\geq$30 g/l or $\geq$10% decrease in the hematocrit and postprocedural arteriovenous fistula.

Patient characteristics, anticoagulation medication (heparin, vitamin K antagonists, GPI, aspirin, clopidogrel) and interventional information (sheath diameter, type of intervention, time of procedure, operator) were recorded for all patients and stored in a validated custom-made database.

Statistical methods

All data were stored in a validated custom-made database. Datasets were inspected prior to analysis for outliers and inconsistencies. Continuous variables were checked for normality. Continuous variables are described as mean ± standard deviation and compared using the student's *t* test if normally distributed. The median, upper and lower quartiles are reported for non-normally distributed continuous variables and the non-parametric Wilcoxon Rank Sum Test was used. Categorical variables are presented as counts and percentages and Fisher's exact test was used in all cases. A two-sided p value of 0.05 is considered significant. Missing data were either coded as a separate category for multivariate analysis, or were imputed using the estimated maximum likelihood algorithm for unrestricted general location model [15]. When continuous variables were converted to categorical variables the cut-off value used was determined by ROC analysis. A generalized linear model for logistic regression was used for univariate and multivariate analyses. Variables which achieved a value of <0.1 in univariate analyses were entered into multivariate models. Interaction terms were entered as long as appropriate based on clinical reasoning for the multivariate analysis. Strata were built for continuous variables that were not normally distributed. For final model selection a step-wise backward selection based on the model log-likelihood ratio was used. Statistical analyses were conducted using the R-Programming language [16].

Results

During a period of 12 months, 4,653 transfemoral cardiac catheterization procedures were performed. Table 1 summarizes baseline characteristics of the study group of which 2,077 (44.6%) received MC and 2,576 (55.4%) VCD to achieve hemostasis. The access site-related vascular complication rate was equivalent in both groups (3.4% manual compression, 3.2% VCD use, p = n.s.).

Major vascular complications were predominantly pseudoaneurysms and hematoma standing for more than 80% of all complications (Table 2). The occurrence of pseudoaneurysms was significantly higher (MC 2.3%, VCD 1.3%, p = 0.01), and the occurrence of hematoma significantly lower (MC 2.2%, VCD 3.5%, p = 0.008) in the MC group compared with the VCD group.

Vascular complications of both, the MC and the VCD group, were subsequently evaluated separately for patients with diagnostic catheterization, elective PCI or procedures related to acute NSTEMI/STEMI. The results are shown in Fig. 1; complication rates for MC and VCD were comparable in the diagnostic catheterization group. In the elective PCI group MC was accompanied with significant higher complication rates (MC 7.7% vs. VCD 3.2%, p = 0.003). In the NSTEMI/STEMI cases MC was associated with lower complication rates. Table 3 subsumes the different complications in detail.

Multivariate analysis revealed different predictors for access site-related vascular complications as shown in Table 4. In the diagnostic and elective PCI group the administration of coumarin was the strongest predictor for vascular complications. In the NSTEMI/STEMI group application of GPI and VCD use was linked to vascular complications.

Table 1 Baseline characteristics

	MC (n = 2,077)	VCD (n = 2,576)	p
Age (y)	66.17 ± 11.7	64.0 ± 11.6	<0.001
Female: sex	33.5%	28.1%	<0.001
BMI (kg/m^2)	27.6 ± 5.9	27.5 ± 5.2	N.s.
RRsys (mmHg)	137.7 ± 26.7	141.0 ± 27.0	<0.001
RRdias (mmHg)	68.9 ± 13.1	69.1 ± 13.2	N.s.
Chronic renal insuff.	12.7%	9.2%	<0.001
Diabetes	24.3%	18.2%	<0.001
Coumarin	12.3%	9.4%	0.003
ASS	85.8%	86.5%	N.s.
Clopidogrel	56.2%	54.5%	N.s.
GPI	7.5%	12.4%	<0.001
Arterial sheath size ≥7F	7.7%	8.7%	N.s.
Venous sheath	19.7%	12.0%	N.s.

Table 2 Vascular complications I

	MC (n = 2,077)	VCD (n = 2,576)	p
Total	88	191	<0.001
Major Compl.	70	83	N.s.
Operation	5	8	N.s.
Infection	1	4	N.s.
Hematoma	46	91	0.008
TIMI minor	11	35	0.004
TIMI major	2	8	0.117
TIMI minor + major	13	43	0.001
Retroperitoneal hematoma	0	2	N.s.
Pseudoaneurysm	47	33	0.01
AV-Fistula	14	3	0.002

Discussion

The present study was designed to prospectively investigate the incidence and predictors of access site-related

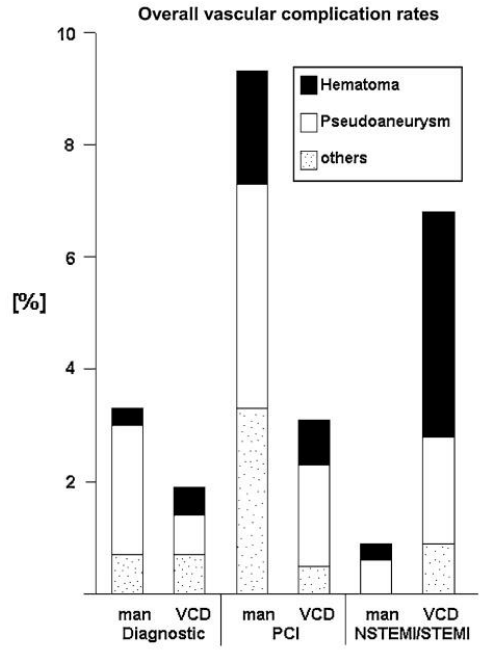

Fig. 1 Overall vascular complication rates

vascular complications with the Angio-Seal™ VCD in a large number of consecutive patients, including elective cardiac catheterizations as well as emergency catheterizations in NSTEMI/STEMI. The major findings of this study are as follows: (1) the use of VCD in acute NSTEMI/STEMI is associated with a significantly higher bleeding rate (2) the strongest predictor for access-site related vascular complications in NSTEMI/STEMI is the use of VCD.

Table 4 Multivariate prediction model for vascular complications

Predictors of vascular complications	OR	95% CI	*p* value
Diagnostic catheterization			
Age >68 (y)	1.91	1.12–3.26	0.02
Female: sex	2.38	1.44–3.95	0.0008
RRsys >150 (mmHg)	1.65	1.0–2.7	0.05
Coumarin	2.90	1.67–5.07	0.0002
Chronic renal insufficiency	2.24	1.18–4.28	0.01
Elective PCI			
Age >68 (y)	2.10	1.05–4.18	0.03
RRsys >150 (mmHg)	1.91	0.98–3.70	0.056
Coumarin	2.60	1.2–5.6	0.01
VCD	0.43	0.22–0.83	0.01
NSTEMI/STEMI			
Female sex	2.40	1.14–5.10	0.02
BMI <25 (kg/m^2)	1.95	0.96–3.95	0.06
RRsys >150 (mmHg)	1.96	0.90–4.25	0.09
GPI	4.63	2.10–10.20	0.0001
VCD	7.52	2.30–25.00	0.001

Incidence of access site-related vascular complications

The overall access site-related vascular complication rate in our study was 3.3% which is low for a "real-world-setting". Rates of 8–9.3% access site-related vascular complications have been reported by Dangas and Chandrasekar [3, 17]. While a general trend towards less vascular complications has been reported [14], we attribute our low complication rate to smaller sheath sizes, tighter control of heparin use by ACT-measuring and predefined sheath removal strategies. Those procedures contained a femoral

Table 3 Vascular complications II

	Diagnostic cases (n = 2,772)			Elective PCI cases (n = 960)			NSTEMI/STEMI cases (n = 921)		
	MC (n = 1,429)	VCD (n = 1,343)	p	MC (n = 299)	VCD (n = 661)	p	MC (n = 349)	VCD (n = 572)	p
Total	50	65	0.08	28	57	N.s.	10	69	<0.001
Total major compl	44	26	0.06	23	21	0.003	3	36	<0.001
Operation	2	5	N.s.	3	1	0.09	0	2	N.s.
Infection	0	1	N.s.	1	1	N.s.	0	2	N.s.
Retroperitoneal hematoma	0	1	N.s.	0	0	N.s.	0	1	N.s.
Hematoma TIMI minimal	19	18	N.s.	6	11	N.s.	10	27	N.s.
Hemat. TIMI minor	3	4	N.s.	5	4	N.s.	1	19	<0.001
Hemat. TIMI major	1	3	N.s.	1	1	N.s.	0	4	N.s.
Pseudoaneurysm	33	10	<0.001	12	12	0.07	2	11	N.s.
AV-Fistula	8	2	N.s.	6	1	0.005	0	0	N.s.

angiogram at the end revealing a sheath insertion point above the inferior epigastric artery, significant femoral arterial disease and nonfemoral artery sheath insertion, all associated with an increased risk of complications [19–22]. Eventhough routine performance of femoral angiograms without implications could not be shown to reduce complication rates in a retrospective study [18], knowledge of the situation with consecutive adaption of the sheath removal strategy led in our study to low complication rates even in "high-risk-sticks".

The present study found no significant difference for access site-related vascular complication rates between MC and VCD. Additional subgroup analyses of patients with diagnostic catheterizations, elective PCI and catheterization for acute NSTEMI/STEMI revealed higher vascular complication rates in patients undergoing elective PCI compared to patients undergoing elective diagnostic catheterizations, a result which has been reported before [3, 6, 7].

VCD use in elective PCI was associated with a lower complication rate than MC, an observation which was reported in meta-analyses [9, 11] and proved in recently published large registries [13, 14], even though the use of VCD is associated with an increased risk of lower limb ischemia/arterial stenosis/device entrapment in the artery and the need for vascular surgery [12, 23, 24]. The most salient difference between the present study and others is that we have exclusively used the Angio-Seal^{TM} VCD in a large, unselected and consecutive cohort, while other studies have employed up to five types of VCDs or smaller cohorts.

Catheterization for acute NSTEMI/STEMI led to major complications in 4.2% of patients. In these patients use of VCD was associated with a significant rise of complications. In this cohort use of GPI, which could be shown as predictor for local vascular complications [4, 5, 25], and commonly impeached vascular complications was certainly more frequent. Nevertheless, use of VCD itself could be shown as independent predictor for local vascular complications in these patients. There are only little data on the risk of local vascular complications in NSTEMI/STEMI patients after application of VCD. Gutierrez et al. [26] compared complication rates in patients undergoing primary PCI with and without receiving thrombolysis and VCD. They demonstrated that major bleeding complications were independent of whether thrombolysis was given. However, this study included only a small cohort of 85 patients, 65 treated with the Angio-Seal^{TM} VCD and 20 with another device collected, retrospectively; a MC control group is missing and complication rates are not attributed to the different VCDs.

Use of VCD in patients treated with GPI during rescue angioplasty was studied by Boccalandro [27]. In total, 162 VCD and 100 MC patients were studied, 70 of them with the Angio-Seal^{TM} device. Similar complication rates for MC and VCD were reported. Compared with 196 matched elective PCI patients no differences in local vascular complication rates were reported, which is in contrast to our findings. Although comparable definitions of major complications were applied, complication rates were threefold higher in the study by Boccalandro compared with our findings. This might be explained by the period of data collection starting in 1998, nearly one decade before our data acquisition took place. General trend towards less vascular complications after cardiac catheterizations in the past decades has been reported due to more attention to risk factors and optimizing access site management [14].

Bleeding complications

The recognition and evaluation of adverse bleeding events are complicated by various definitions and scales used in clinical trials and registries. The most common definitions of bleeding severity were developed for trials of fibrinolytic therapy [28, 29]. Whether these definitions remain clinically relevant for patients with acute coronary syndromes is unclear. A standard definition is still pending. A commonly used definition for local vascular complication rates is the TIMI classification utilized by ourselves in the present study.

Independent of its definition, bleeding has been related to short- and long-term adverse outcomes, including mortality, in patients with ACS and undergoing PCI [30, 31]. The 30-day risk of death or MI has been shown to be increased with all three levels of TIMI bleeding [32]. Moreover, in the REPLACE-2 trial the unadjusted 30-day mortality was significantly higher even in patients with TIMI minor bleedings [33]. Therefore, the classification of local vascular complications in our study includes TIMI minor and TIMI major bleedings as major complications.

Regarding the bleeding complications a significant increase was observed with VCD use, for the total study population. Within the particular subdivisions, diagnostic catheterization, PCI and NSTEMI/STEMI, the difference between MC and VCD remained only significant in the NSTEMI/STEMI group in which hematomas caused most of the major complications. Our perception is that bleedings associated with VCD are an underestimated risk due to focusing on TIMI major bleedings in most of the published studies.

Predictors for vascular complications

Risk factors for access site-related vascular complications can be divided into the categories non-modifiable and modifiable. Age, gender, weight, renal insufficiency,

diabetes and hypertension are well established non-modifiable risk factors, procedural characteristics as well as choice, dosage and duration of antithrombotic therapy are modifiable risk factors for vascular complications [34, 35].

First of all our study verified the well-known established risk factors for access site-related vascular complications. Application of VCD led to a decrease in complication rates for elective PCI patients. This finding is in concordance with large recent registries [13, 14, 21]. Interestingly, VCD led to significant rise in complication rates in NSTEMI/STEMI patients; in multivariate analysis its application turned out to be the strongest predictor for access site-related vascular complications. Those complications consist predominantly in bleeding complications as discussed above.

Study limitations

All patients undergoing cardiac catheterization procedure in our hospital through the transfemoral access were included in this study. No randomization to manual compression or use of VCD took place.

We did not evaluate vascular complications which developed after discharge from the hospital. Therefore, complications which developed at a later time point may have been overseen.

Clinical implications

Bleeding from the puncture site is an increasingly recognized risk factor for death and ischemic events following cardiac catheterization [30]. The focus on access site-related vascular complications has increased due to improved safety of the cardiac procedure itself. Over the past decade multiple strategies to reduce vascular complications in the catheterization laboratory took place, including downsizing sheath sizes, use of VCD in elective settings and minimizing heparin dosages during the procedures [9, 11, 36, 37]. All these strategies may have contributed to the decrease in access site related vascular complication rates with the femoral artery access [14]. Minimizing the risk of bleeding seems to be a necessary step in the management of patients undergoing both elective and emergency cardiac catheterization [38], but there is no proof that reducing bleeding events improves outcomes. Our observation that VCD is associated with a higher risk of bleeding complications in patients undergoing emergency PCIs in NSTEMI/STEMI should be consequently peered and procedural strategies adjusted.

Conflict of interest The authors declare that they have no conflict of interest.

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Effect of preinterventional ultrasound examination on frequency of procedure-related vascular complications in percutaneous coronary interventions with transfemoral approach

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Am J Cardiol. 2011 Nov 1;108(9):1203-6

Lokale Gefäßkomplikationen im Bereich der Punktionsstelle sind die häufigsten unerwünschten Ereignisse im Rahmen von Koronarinterventionen mit nachweislich erhöhter Morbidität und Mortalität. Eine Ursache für diese Komplikationen kann bei Verwenden des transfemoralen Zugangsweges eine Punktion außerhalb des mittleren Segmentes der Arteria femoralis communis sein. Untersucht wurde der Einfluss einer am Vortag der Untersuchung durchgeführten Ultraschalluntersuchung mit Markierung der individuellen Gefäßanatomie auf die Komplikationsraten. Diese konnten durch die zuvor durchgeführte Ultraschalluntersuchung signifikant gesenkt werden.

Effect of Preinterventional Ultrasound Examination on Frequency of Procedure-Related Vascular Complications in Percutaneous Coronary Interventions With Transfemoral Approach

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Vascular complications are the most frequent adverse events associated with percutaneous coronary interventions (PCIs) leading to an increase in morbidity and mortality. Puncture of the common femoral artery in its middle segment is proved to decrease the risk of procedure-related vascular complications. Real-time ultrasound-guided puncture of the vessel is effective to decrease access site-related vascular complications but complex to perform. We evaluated whether an ultrasonic preinterventional examination of the femoral puncture site and skin marking of anatomic structures and specific vascular characteristics results in a decrease of access site-related vascular complications in PCIs with transfemoral access. Over a period of 12 months we prospectively examined all puncture sites before elective PCIs with transfemoral access (n = 848) using ultrasound. Presence, extent, and location of plaques and stenoses and exact location of bifurcation of the femoral artery were marked by a sonographer on the skin to guide the interventionists in vascular puncture. Postinterventional access site ultrasound was performed to determine possible access site-related complications. Frequency of vascular access site complications was compared to a control cohort (n = 1,027) that did not undergo ultrasound examination before intervention. With ultrasonic vascular access site management the rate of access site-related vascular complications was decreased from 4.2% to 1.9% (odds ratio 0.44, 0.23 to 0.80, p = 0.005). In conclusion, preinterventional ultrasonic access site examination and skin marking decreases the risk of vascular complications in elective PCI with femoral access. **(Am J Cardiol 2011;108:1203–1206)**

The aim of this study was to evaluate whether a simple and rapidly performed preinterventional ultrasound examination of the femoral access site with skin marking of the preferred puncture site leads to a decrease of access site-related vascular complications.

Methods

In this single-center study all elective percutaneous coronary interventions (PCIs) performed with a transfemoral access from March 2008 through February 2009 were included. This relates to 848 access sites. Anticoagulation after sheath insertion was obtained using unfractionated heparin with a target activated clotting time of 250 to 300 seconds or 200 to 250 seconds if used in conjunction with glycoprotein IIb/IIIa inhibitor (GPI). Patients received GPI at the discretion of the treating physician according to standard protocol with abciximab or eptifibatide. Patients were given aspirin 100 mg/day and clopidogrel (300 or 600 mg as a loading dose followed by 75 mg/day) if stents were placed.

On the day before PCI all patients received clinical and ultrasound examinations of the groin and legs. Pulses of the femoral, popliteal, and tibial arteries were palpated and the groin auscultated. Subsequently an ultrasound examination of the groin was performed with measurement of the diameter of the common femoral artery and flow measurement by Doppler of the common femoral artery and proximal superficial femoral artery. The site of the femoral bifurcation and presence, extent, and location of plaques and stenosis were directly marked on the skin of the groin (Figure 1). In obese patients the bifurcation was marked laterally on the skin of the groin to avoid skin-marker displacement during intraoperative manipulation. Plaque presence in obese patients was indicated only by an exclamation point to warn the interventionist.

The control group included all patients undergoing elective PCIs in a 12-month period before performing the study. Pre- and postinterventional access site managements in this group were identical to the study group except for preinterventional ultrasound of the groin. Procedural techniques of PCI including antithrombotic therapy, sheath removal, and access site evaluation after the procedure were identical between the control and study groups.

During PCI localization of the puncture site was at the discretion of the operator. All operators were experienced interventional cardiologists with ≥300 arterial punctures

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doi:10.1016/j.amjcard.2011.06.032

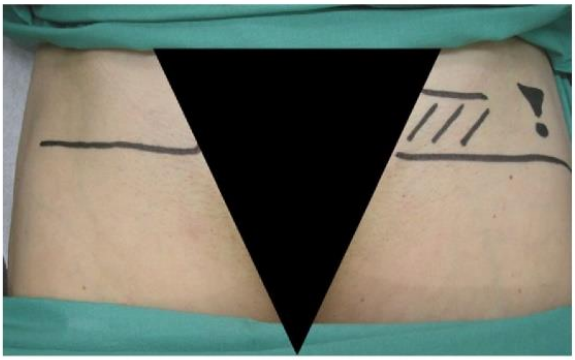

Figure 1. Example of preinterventional skin marking indicating the bifurcation *(horizontal line)*, ventral plaque *(diagonal lines)*, and dorsal plaque *(exclamation point)*.

Table 1
Baseline characteristics

Variable	Control Group (n = 1,027)	Study Group (n = 848)	p Value
Age (years)	66.0 ± 10.9	67.7 ± 10.3	<0.001
Women	26.8%	24.9%	NS
Body mass index (kg/m^2)	27.4 ± 4.2	28.6 ± 8.5	<0.001
Systolic blood pressure (mm Hg)	142.7 ± 27.2	139.5 ± 24.8	0.01
Diastolic blood pressure (mm Hg)	68.1 ± 12.7	68.2 ± 13.7	NS
Chronic renal insufficiency	12.3%	14.4%	NS
Diabetes mellitus	38.2%	37.4%	NS
Warfarin use	11.2%	12.9%	NS
Aspirin	93.7%	92.5%	NS
Clopidogrel	93.6%	99.9%	<0.001
Glycoprotein IIb/IIIa inhibitors	11.3%	5.4%	<0.001
Arterial sheath size ≥7Fr	9.3%	2.0%	<0.001
Venous sheath	23.2%	20.8%	NS

annually. Sheath localization was documented by angiography. The recommended method of sheath removal was vascular closure device (VCD) deployment immediately after the procedure. The VCD Angio-Seal (St. Jude Medical, St. Paul, Minnesota) was the only VCD used during the entire study period. Patients did not undergo arterial closure with a VCD if (1) the arteriotomy site was ≤2 cm proximal to the bifurcation of the common femoral artery, below the femoral bifurcation, or above the inferior epigastric artery; (2) the common femoral artery had a vessel diameter ≤6 mm; (3) extensive calcification or plaque formation was present in the area of sheath insertion; and (4) extensive scar tissue was present at the access site. All operators had received training and had used the device in ≥50 cases before the study started. Sheath removal with manual compression (MC) took place in all patients with contraindications for VCD. MC sheath removal occurred when the activated clotting time was ≤150 seconds and a compression bandage was applied. Ambulation was initiated 4 hours after the VCD was placed and 6 hours after MC. Effective anticoagulation or administration of GPI

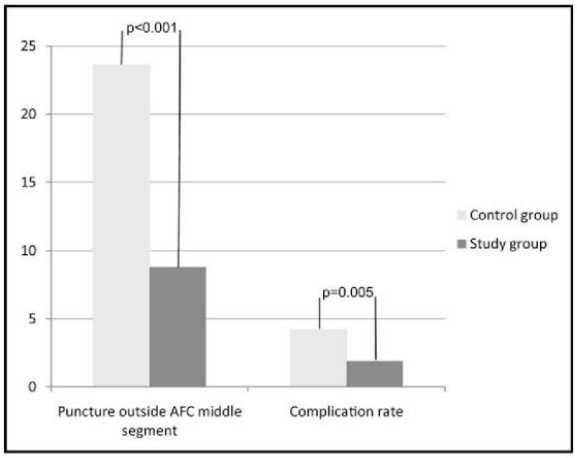

Figure 2. Influence of preinterventional ultrasound on puncture site localization and complication rate.

Table 2
Vascular complications

	Control Group (n = 1,027)	Study Group (n = 848)
Total	85 (8.3%)	62 (7.3%)
Major complications	43 (4.2%)*	16 (1.9%)*
Operation	0	2 (0.2%)
Infection	2 (0.2%)	0
Thrombolysis In Myocardial Infarction minor	12 (1.2%)	6 (0.7%)
Thrombolysis In Myocardial Infarction major	2 (0.2%)	0
Thrombolysis In Myocardial Infarction minor + major	14 (1.4%)	6 (0.7%)
Transfusion	1 (0.1%)	2 (0.2%)
Retroperitoneal hematoma	0	1 (0.1%)
Pseudoaneurysm	24 (2.3%)	11 (1.3%)
Arteriovenous fistula	7 (0.7%)	2 (0.2%)

* p = 0.005.

was followed by 12-hour bandaging even if patients received a VCD.

Access site evaluation after the interventional procedure was carried out consistently in all patients in the 2 groups. Postinterventional assessment of the puncture site included clinical examination immediately after the catheterization procedure and after removal of the compression bandage. Examinations before the catheterization procedure and after removal of the compression bandage were performed by the same physician to ensure that changes were perceived. Any changes or abnormalities at the puncture site were reported to a vascular specialist resulting in vascular ultrasound and/or supplementary examinations such as computed tomography.

The following complications were recorded: bleeding defined as external blood loss requiring MC; oozing requiring light manual pressure; ecchymosis >5 cm in the soft tissue of the upper thigh; hematoma formation; retroperitoneal extension of hematoma, vessel obstruction, or closure; pseudoaneurysm; arteriovenous fistula confirmed by clinical

Table 3
Prediction model for vascular complications

Predictors	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Preinterventional ultrasonography	0.53	0.31–0.90	0.02	0.45	0.24–0.81	0.008
Vascular closure device	0.48	0.29–0.79	0.004	0.48	0.28–0.83	0.008
Male gender	2.22	1.34–3.70	0.002	2.27	1.30–3.85	0.003
Systolic blood pressure >140 mm Hg	1.90	1.15–3.13	0.01	1.79	1.04–3.08	0.04
Warfarin use	2.74	1.55–4.86	0.0005	3.36	1.83–6.15	<0.0001
Glycoprotein IIb/IIIa inhibitors	3.08	1.67–5.70	0.0003	3.17	1.63–6.17	0.0007
Renal insufficiency	1.85	1.01–3.39	0.05			
Diabetes mellitus	0.89	0.51–1.54	0.68			
Age >68 years	1.78	1.06–2.98	0.028			
Body mass index >25 kg/m^2	0.90	0.52–1.55	0.71			
Additional venous sheath	1.06	0.59–1.91	0.84			

examination, vascular ultrasonography, or computed tomography; infection of puncture site; decrease in hemoglobin concentration; need for blood transfusion; and need for surgery. Major vascular complications were defined as need for surgery, infection requiring intravenous antibiotics or surgical lancing, retroperitoneal hemorrhage, bleeding requiring blood transfusion, pseudoaneurysm, hematoma associated with a decrease in hemoglobin concentration by ≥30 g/L or ≥10% decrease in hematocrit, and postprocedural arteriovenous fistula.

Patient characteristics, anticoagulation medication (heparin, warfarin, GPI, aspirin, clopidogrel), and interventional procedure characteristics (sheath diameter, operator, additional sheaths, puncture site) were recorded in all patients.

All data were stored in a validated custom-made database. Datasets were inspected before analysis for outliers and inconsistencies. Continuous variables were checked for normality using the Shapiro–Wilke test. Continuous variables are described as mean ± SD and were compared using Student's *t* test if normally distributed. Median and upper and lower quartiles are reported for non-normally distributed continuous variables and the nonparametric Wilcoxon rank-sum test was used. Categorical variables are presented as counts and percentages and Fisher's exact test was used in all cases. A 2-sided p value of 0.05 was considered statistically significant. A generalized linear model for logistic regression was used for univariate and multivariate analyses. Variables with a p value ≤0.10 in univariate analyses were entered into multivariate models. Variables for univariate analysis including age, gender, weight, diabetes, hypertension, chronic renal insufficiency, anticoagulants, ultrasonic-guided puncture, use of VCD, and sheath size were predefined and selected on clinical grounds. Interaction terms were entered into the multivariate model based on clinical reasoning. Strata were built for continuous variables that were not normally distributed. In addition, all continues variables were dichotomized using the median as the cutoff unless a clinically defined cutoff was available (e.g., body mass index ≥25 kg/m^2). For final model selection a stepwise backward selection based on the model log-likelihood ratio was used. Statistical analyses were conducted using the R statistical programming language.[1]

Results

During a period of 12 months 848 PCIs with a transfemoral access site were performed. Table 1 presents baseline characteristics of the study group (n = 848) compared to the control group (n = 1,027). Frequency of inappropriate punctures below the femoral bifurcation or above the inferior epigastric artery was decreased from 23.6% to 8.8% with ultrasonic-guided vascular access site management (odds ratio [OR] 0.31, 95% confidence interval [CI] 0.42 to 0.23, p <0.001) and, hence, the VCD application rate increased significantly from 68.7% to 75.1% (OR 1.37, 95% CI 1.12 to 1.70, p = 0.002). Major vascular complications were significantly decreased in the study group (1.9% in study group vs 4.2% in control group, OR 0.44, 95% CI 0.23 to 0.80, p = 0.005; Figure 2). Table 2 presents the frequency of different access site-related vascular complications. Uni- and multivariate analyses identified use of preinterventional ultrasonography, use of VCD, gender, blood pressure, warfarin use, and use of GPI as independent predictors of access site-related vascular complications. No statistically significant interaction was present. Performance of preinterventional ultrasound and use of VCD were found to be associated with decreased risk of complications (Table 3).

Discussion

Over a period of 12 months we implemented a preinterventional ultrasound examination of the puncture site in daily practice and verified a significant decrease of access site-related vascular complications in elective PCIs with transfemoral access.

Despite a decrease in access site-related vascular complications during the previous decade,[2] vascular access-related complications after percutaneous procedures remain common causes of morbidity and mortality.[3,4] To decrease the rate of access site-related vascular complications different strategies have been developed. VCDs have demonstrated an overall safety comparable to MC.[5] Recently published registry data have shown even a decrease of vascular complications using VCD compared to MC.[2,6] The known association between high sticks and retroperitoneal hemorrhage[7,8] and low sticks with pseudoaneurysms and arteriovenous fistulas[9] made compelling arguments for optimizing

the access site to prevent complications. There is evidence for fairly low complication rates if location of the puncture site is in the common femoral artery in its middle segment.[10] Optimizing localization of the puncture site including guidance by anatomic landmarks,[11] fluoroscopy,[12] and ultrasound[13,14] has been proposed. Traditionally real-time ultrasound guidance is performed but the difficulty to maintain sterility, to manage the supplementary equipment, and to handle the uncommon setting has resulted in low acceptance by most interventional cardiologists. Prospective randomized studies have demonstrated no or little difference in complication rates between ultrasound-guided puncture and conventional puncture techniques.[15] Because of the great effort and moderate benefit for patients at low risk, the authors consider ultrasound guidance for any patient at high risk for a difficult access or complications.[14]

The major advantages of ultrasound-guided puncture without the significant efforts associated with performance in the catheterization laboratory are obtained by routine preinterventional examination of the puncture site as performed in this study. The major advantages are that (1) no additional time or equipment is required in the catheterization laboratory; (2) the examination is noninvasive, available, and feasible with minimal expenditure of time; and (3) skin markings of the bifurcation of the common femoral artery and those of the presence, extent, and location of plaques support interventionists in optimizing localization of the puncture without giving up familiar techniques such as anatomic landmark guidance or fluoroscopic guidance.

Because of the study design all consecutive patients with PCI were included and no randomization took place. Compared to the control group, which was obtained before the study group during an identical period, the absolute number of patients receiving elective PCI by the transfemoral approach had decreased. This is in contrast to an increasing number of emergency PCIs during the study period. However, ultrasound study of the puncture site could not be guaranteed consistently for emergency PCI cases. Thus, these patients were not included in the control and study groups.

In conclusion, a transfemoral access site approach with decreased vascular complications can be achieved by preinterventional ultrasound examination as performed in this study. Thus, there exists an easy tool to increase the safety of cardiac catheterizations using the transfemoral approach.

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Evaluation of a structured training program for arterial femoral sheath removal after percutaneous arterial catheter procedures by assistant personnel

Stegemann E, Busch L, Stegemann B, Lauer T, Hoffmann R, Heiss C, Kelm M

Am J Cardiol. 2015 Apr 1;115(7):879-83

Hämostase nach Herzkatheteruntersuchungen kann durch manuelle Kompression, die Verwendung externer Kompressionsgeräte oder die Verwendung von Verschlusssystemen erreicht werden. Trotz technischer Verbesserungen der Systeme zur externen Kompression und sofortigem Verschluss, müssen weiterhin zahlreiche, zeitaufwendige manuelle Kompressionen durchgeführt werden. In Deutschland wird diese Arbeit üblicherweise von Ärzten übernommen, Inhalt dieser Untersuchung war ein Trainingsprogramm für Rettungsassistenten, welches im Rahmen der täglichen Routine implementiert wurde. Die Einführung war ohne vermehrte Komplikationsraten durchführbar, die manuelle Kompression durch Hilfspersonal sicher und effektiv.

Evaluation of a Structured Training Program for Arterial Femoral Sheath Removal After Percutaneous Arterial Catheter Procedures by Assistant Personnel

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After cardiac catheterization procedures, arterial closure can be achieved by manual compression (MC), using external mechanical compression devices, or by applying vascular closure devices (VCDs) with comparable vascular access site–related complication rates. The aim of the present study was to assess vascular access site–related complications during the implementation of structured sheath removal and MC by paramedics after catheterization procedures. After an observational phase of 3 months to assess the baseline complication rate, a structured 4-level training program was implemented to train assistant personnel, in this case paramedics, in the management of sheath removal by MC. Access site–related complication rates after sheath removal were assessed prospectively and MC by paramedics compared with MC by physicians and application of VCDs. To account for imbalances in procedure- and patient-related risk factors of access-site complications, propensity score–based matching analysis was performed (*ClinicalTrials.gov* identifier NCT00825331). All consecutive percutaneous transfemoral arterial cardiac catheterization procedures were prospectively assessed over a period of 8 months (n = 3,503). MC was performed in 2,315 cases, of which 180 were performed by paramedics and 2,135 by physicians; VCDs were applied in 1,188 procedures. Rates of access site–related complications were significantly lower for paramedics compared with physicians (p = 0.03) and similar between paramedics and VCDs (p = 0.77). In conclusion a structured program for paramedics to be trained in sheath removal after percutaneous cardiac catheterization procedures can be readily implemented during clinical routine with low in-hospital complication rates. **(Am J Cardiol 2015;115:879–883)**

Despite increasing application of radial access for percutaneous arterial catheter procedures, many interventions are still performed via the transfemoral approach, for various reasons. Achieving hemostasis by manual compression (MC) is a time-consuming, unpopular activity for physicians. Alternatives, especially vascular closure devices (VCD), are frequently applied, leading to significant shortening of time to achieve hemostasis and a reduction of access site–related vascular complications at the price of higher costs and sometimes detrimental severe complications, such as vessel occlusions.[1] In Germany, sheath removal and MC are commonly performed by physicians; delegation to assistant personnel remains unusual. We developed a training program tailored for paramedics, enabling them to handle access site and sheath removal after percutaneous arterial procedures independently. Implementation and evaluation of this training program were carried out in the context of the present prospective observational study.

Methods

All consecutive transfemoral catheterization procedures at our clinic were prospectively monitored. After a period of 3 months, to assess baseline complication rates, the structured training program for paramedics was implemented. The study protocol was evaluated and approved by the local ethics committee, and the study design was registered at a public depository (*ClinicalTrials.gov* identifier NCT00825331).

The training program included 4 risk levels for access site–associated complications, on the basis of anticoagulation status and sheath size. Level 1 included a single platelet aggregation inhibitor and sheath sizes of ≤5Fr, representing the patient group with the lowest expected access site–associated complication rate. In level 2, a sheath size of 6Fr and dual platelet aggregation inhibition was allowed. The next level augmented up to 7Fr sheaths, and in addition to dual platelet aggregation inhibition, the application of glycoprotein IIb/IIIa inhibitors or the presence of oral anticoagulation was allowed. Patients in whom the highest access site–associated complication rates were expected, including sheath sizes of ≥8Fr and dual platelet aggregation inhibition as well as oral anticoagulation, constituted level 4. If only 1 single criterion of a level was

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Dr. Kelm is funded by Deutsche Forschungsgemeinschaft (Grants KE405/5-1, IRTG1902 TP9, and FOR809 TP7).

See page 883 for disclosure information.

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http://dx.doi.org/10.1016/j.amjcard.2015.01.012

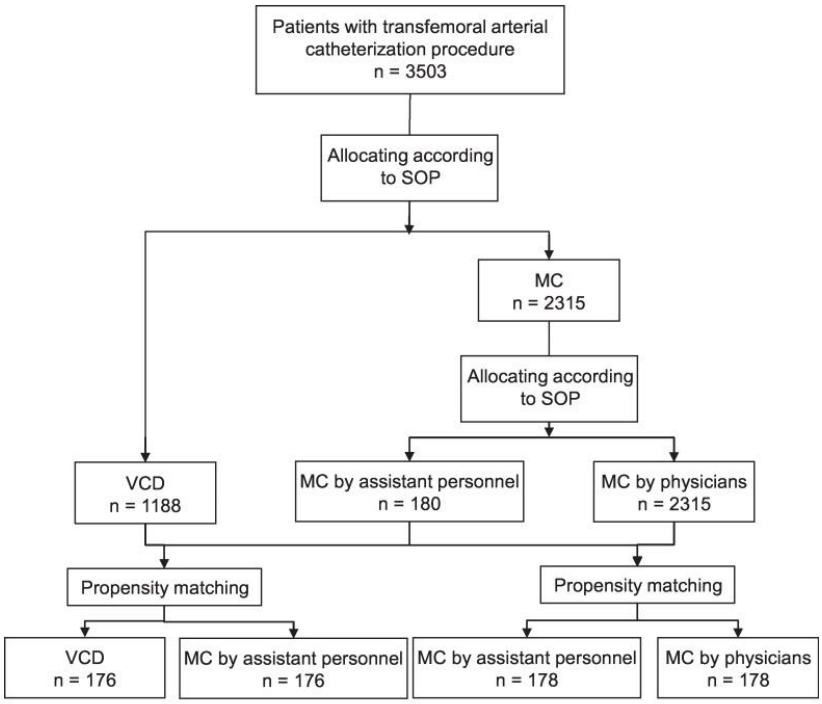

Figure 1. Flow diagram of access site management. SOP = standard operating procedures.

fulfilled, the patient was assigned to the higher level; for example, patients with dual platelet aggregation inhibition as well as oral anticoagulation were assigned to level 4 regardless of the sheath size used.

Sheath removal by the paramedics started with 10 sheath removals in level 1 patients under direct supervision of an experienced physician. Once these 10 removals were successfully completed, the paramedics were allowed to independently perform level 1 patient sheath removals and were eligible for 10 supervised sheath removals in level 2 patients. This approach was repeated at each level, permitting the paramedics to perform increasingly complex sheath removals in patients at higher risk in a stepwise fashion. During the entire study period, the access site was examined before sheath removal and after MC by a physician to ensure successful compression of the puncture site.

During the whole study period, sheath removal was carried out according to standard operating procedures of the clinic. A flow diagram of access site management is shown in Figure 1. MC was performed for sheaths $\leq$5Fr. All sheaths $\geq$6Fr received VCDs, provided that no contraindications applied. To assess contraindications for VCD insertion, all patients underwent angiographic evaluation of the external iliac, common femoral, and proximal superficial femoral arteries. Contraindications were as follows: (1) site of arteriotomy $\leq$2 cm proximal to the bifurcation of the common femoral artery, below the femoral bifurcation, or above the inferior epigastric artery; (2) common femoral artery vessel diameter $\leq$6 mm; (3) extensive calcification or plaque formation in the area of sheath insertion; and (4) extensive scar tissue at the access site. Clinical evaluation of the puncture site was performed before and immediately after sheath removal as well as after removal of the compression bandage. Any changes or abnormalities at the puncture site were reported to a vascular specialist, resulting in vascular ultrasound and/or supplementary examinations such as CT angiography.

The following complications were recorded: bleeding, defined as external blood loss requiring MC; oozing requiring light manual pressure; ecchymosis >5 cm in the soft tissue of the upper thigh; hematoma formation; retroperitoneal extension of hematoma; vessel obstruction or closure; pseudoaneurysm; arteriovenous fistula confirmed by clinical examination, vascular ultrasonography, or computed tomography; infection of the puncture site; a reduction in hemoglobin concentration of $\geq$30 g/L or a $\geq$10% decrease in hematocrit; need for blood transfusion; and need for surgery.

Major vascular complications were defined as any of the following: need for surgery, infection requiring intravenous antibiotics or surgical lancing, retroperitoneal hemorrhage, bleeding requiring blood transfusion, pseudoaneurysm, hematoma associated with a decrease in hemoglobin concentration of $\geq$30 g/L or a $\geq$10% decrease in hematocrit (according to Thrombolysis In Myocardial Infarction [TIMI] minor bleeding),[2] and postprocedural arteriovenous fistula.

Patient characteristics, anticoagulation medications (heparin, vitamin K antagonists, GPIs, aspirin, thienopyridine), and interventional procedural characteristics (sheath diameter, operator, additional sheaths, and puncture site) were recorded in all patients.

Data were entered and stored in a validated, custom-made database. Statistical analyses were conducted using the R programming language.[3] Continuous variables were checked for normality, and normally distributed variables

Table 1
Baseline characteristics and kind of interventions, unmatched

Variable	MC paramedics (n=180)	MC physicians (n=2135)	p*	VCD (n=1188)	P†
Age (years)	67.3 ± 11.9	68.6 ± 12.0	n.s.	65.9 ± 12.4	n.s.
Women	71 (39.4%)	737 (34.5%)	n.s.	350 (29.5%)	0.017
Body-Mass-Index (kg/m^2)	28.1 ± 5.1	28.3 ± 18.8	n.s.	28.1 ± 5.2	n.s.
Systolic blood pressure (mmHg)	141.4 ± 28.0	140.2 ± 28.8	n.s.	135.9 ± 27.1	0.014
Diastolic blood pressure (mmHg)	70.4 ± 11.6	69.2 ± 13.9	n.s.	70.0 ± 14.4	n.s.
Chronic renal insufficiency	28 (15.5%)	274 (12.8%)	n.s.	95 (8.0%)	0.002
Diabetes mellitus	47 (26.1%)	557 (26.1%)	n.s.	248 (20.9%)	n.s.
Warfarin	25 (13.8%)	270 (12.6%)	n.s.	94 (7.9%)	0.015
Aspirin	130 (72.2%)	1641 (76.9%)	n.s.	991 (83.4%)	<0.001
Clopidogrel	61 (33.8%)	1123 (52.6%)	< 0.001	789 (66.4%)	<0.001
Glycoprotein IIb/IIIa inhibitors	4 (2.2%)	169 (7.9%)	0.005	154 (13.0%)	<0.001
Arterial sheath size ≥7F	2 (1.1%)	3 (0.1)%	0.05	3 (0.2%)	n.s.
Venous sheath	46 (25.6)%	448 (21.0%)	n.s.	185 (15.6%)	0.002
Kind of intervention					
Diagnostic catheterizations	156 (86.7%)	1517 (71.1%)	<0.001	626 (52.7%)	<0.001
Percutaneous Coronary Intervention	1 (0.6%)	232 (10.9%)	<0.001	259 (21.8%)	<0.001
Myocardial infarction (Non-ST-Elevation and ST-Elevation)	9 (5.0%)	334 (15.6%)	<0.001	294 (24.7%)	<0.001
Electrophysiological Study	14 (7.8%)	52 (2.4%)	<0.001	9 (0.8%)	<0.001

* MC paramedics vs. MC physicians.
† MC paramedics vs. VCD.

Table 2
Baseline characteristics and kind of interventions, matched

	MC paramedics (n=178)	MC physicians (n=178)	p*	VCD (n=176)	MC paramedics (n=176)	p†
Age (years)	67.3 ± 11.9	70.0 ± 10.3	n.s.	66.4 ± 11.9	67.5 ± 11.8	n.s.
Women	71 (39.9%)	64 (36.0%)	n.s.	51 (29.0%)	66 (37.5%)	n.s.
Body-Mass-Index (kg/m^2)	28.1 ± 5.1	32.5 ± 6.3	n.s.	28.5 ± 5.5	28.1 ± 5.1	n.s.
Systolic blood pressure (mmHg)	141.4 ± 28.0	140.9 ± 28.0	n.s.	130.4 ± 26.5	142.8 ± 27.7	n.s.
Diastolic blood pressure (mmHg)	70.4 ± 11.6	69.3 ± 14.0	n.s.	67.8 ± 14.5	70.6 ± 11.7	n.s.
Chronic renal insufficiency	28 (15.7%)	30 (16.9%)	n.s.	25 (14.2%)	28 (15.9%)	n.s.
Diabetes mellitus	47 (26.4%)	43 (24.2%)	n.s.	35 (19.9%)	46 (26.1%)	n.s.
Warfarin	25 (14.0%)	33 (18.5%)	n.s.	11 (6.3%)	18 (10.2%)	n.s.
Aspirin	130 (73.0%)	121 (68.0%)	n.s.	144 (81.8%)	126 (71.6%)	0.025
Clopidogrel	61 (34.3%)	77 (43.3%)	n.s	137 (77.8%)	61 (34.7%)	< 0.001
Glycoprotein IIb/IIIa inhibitors	3 (1.7%)	4 (2.2%)	n.s	4 (2.3%)	3 (1.7%)	n.s.
Arterial sheath size ≥7F	2 (1.1%)	2 (1.1%)	n.s.	0 (0.0%)	2 (1.1%)	n.s.
Venous sheath	46 (25.8%)	35 (19.7%)	n.s.	17 (9.7%)	39 (22.2%)	0.002
Kind of intervention						
Diagnostic catheterizations	156 (87.6%)	153 (86.0%)	n.s.	158 (89.8%)	156 (88.6%)	n.s.
Percutaneous Coronary Intervention	1 (0.6%)	2 (1.1%)	n.s.	3 (1.7%)	1 (0.6%)	n.s.
Myocardial infarction (Non-ST-Elevation and ST-Elevation)	9 (5.1%)	13 (7.3%)	n.s.	8 (4.5%)	9 (5.1%)	n.s.
Electrophysiological Study	12 (6.7%)	10 (5.6%)	n.s.	7 (4.0%)	10 (5.7%)	n.s.

* MC paramedics vs. MC physicians.
† MC paramedics vs. VCD.

were compared using Student's *t* test and are described as mean ± SD. The median and upper and lower quartiles are reported for continuous variables not normally distributed, and the nonparametric Wilcoxon's rank-sum test was used. Categorical variables are presented as counts and percentages, and Fisher's exact test was used. Two-sided p values <0.05 were considered statistically significant. Missing data were imputed using additive regressions, bootstrapping, and predictive mean matching from the Hmisc package in R. We performed propensity score–based matching using the nonrandom package in R. Response data were unbalanced and showed quasi-complete separation, as the number of access site–related complications was zero in the paramedic group. Odds ratios and confidence intervals in this situation were calculated using the logistf package in R, implementing penalized profile likelihood-based estimation of confidence intervals.

Results

Over a period of 8 months, 3,503 cardiac catheterizations with the transfemoral approach were performed. Baseline

Table 3
Access site-related complications, unmatched

	All (n=3503)	MC paramedics (n=180)	MC physicians (n=2135)	p*	VCD (n=1188)	p†
Total	225 (6.4%)	6 (3.3%)	148 (6.9%)	0.062	71 (6.0%)	n.s.
Major complications	57 (1.6%)	0	42 (2.0%)	0.072	15 (1.3%)	n.s.
Pseudoaneurysm	44 (1.3%)	0	32 (1.50%)	n.s.	12 (1.0%)	n.s.
AV-fistula	3 (0.1%)	0	2 (0.1%)	n.s.	1 (0.1%)	n.s.
Infection	1 (0.03%)	0	1 (0.1%)	n.s.	0	n.s.
Hematoma	103 (2.9%)	3 (1.7%)	63 (3.0%)	n.s.	37 (3.1%)	n.s.
Retroperitoneal Hematoma	0	0	0	n.s.	0	n.s.
TIMI minor bleeding	12 (0.3%)	0	9 (0.4%)	n.s.	3 (0.3%)	n.s.
TIMI major bleeding	3 (0.1%)	0	2 (0.1%)	n.s.	1 (0.1%)	n.s.
Vessel stenosis/closure	1 (0.03%)	0	0	n.s.	1 (0.1%)	n.s.

* MC paramedics vs. MC physicians.
† MC paramedics vs. VCD.

Table 4
Access site-related complications, matched

	MC paramedics (n=178)	MC physicians (n=178)	p*	MC paramedics (n=176)	VCD (n=176)	p†
Total	6 (3.4%)	12 (6.7%)	n.s.	6 (3.4%)	9 (5.1%)	n.s.
Major complications	0	6 (3.4%)	0.03	0	3 (1.7%)	n.s.
Pseudoaneurysm	0	5 (2.8%)	0.06	0	2 (1.1%)	n.s.
AV-fistula	0	0	n.s.	0	0	n.s.
Infection	0	1 (0.6%)	n.s.	0	0	n.s.
Hematoma	3 (1.7%)	6 (3.4%)	n.s.	3 (1.7%)	3 (1.7%)	n.s.
Retroperitoneal Hematoma	0	0	n.s.	0	0	n.s.
TIMI minor bleeding	0	0	n.s.	0	2 (1.1%)	n.s.
TIMI major bleeding	0	0	n.s.	0	1 (0.6%)	n.s.
Vessel stenosis/closure	0	0	n.s.	0	0	n.s.

* MC paramedics vs. MC physicians.
† MC paramedics vs. VCD.

characteristics and the kind of intervention of the whole study group are listed in Table 1. Because of the structure of the training program, the paramedics performed MC predominantly in lower risk patients. To adjust the imbalanced distribution of known patient- and procedure-associated risk factors for access site–related vascular complications, propensity score matching was performed (Table 2).

The overall access site–related vascular complication rates for the whole study population are listed in Table 3. Table 4 lists the rates of access site–related complications for the matched populations.

Discussion

This study demonstrates that MC after sheath removal by paramedics is a safe and effective method to achieve hemostasis after cardiac catheterization procedures. Implementation of sheath removal by assistant personnel supported by a structured program can be accomplished during clinical routine, with low complication rates.

Achieving hemostasis after cardiac catheterization procedures is an important component of the procedure because of the consequences of complications on long-term patient outcomes.[4,5] Rates of access site–related vascular complications depend on patient-related factors that cannot be modified and procedure-related factors that can be changed, including puncture technique, sheath size, and the modality of arterial closure.[4,6–8] The radial access, which is universally believed to decrease all vascular access site complications, is increasingly applied but with the addition of the necessity to switch periodically to the transfemoral approach. In the groin, achieving hemostasis by MC of the puncture site is the oldest technique, with proved safety and efficacy in many surveys.[9,10] Complication rates depend on the duration of compression, with lower complication rates for longer compression times.[11] Because MC is a time-consuming and sometimes dreadful task for many physicians, alternative methods to achieve arterial closure were sought. Early on, external compression devices were developed and evaluated.[12] These devices were shown to be as effective and safe as MC performed by trained physicians, provided that patients remain in bed as long as the devices were applied. However, optimal placement of the device requires frequent practice, patient convenience may be hampered, and sufficient compression cannot be achieved adequately in many obese patients. As a next step, VCDs were developed in the 1990s as a rapid, easy, and comfortable tool with all-around patient and physician satisfaction.[13] The effectiveness and safety of VCDs were optimized, resulting in complication rates comparable with

those of MC.[14,15] Despite their relatively high price, VCD were quickly accepted as replacements for the time-consuming compression procedure and are widely used, thanks to high comfort for physicians and patients. With the wider use of VCDs, new serious device-associated vascular complications, such as vascular stenoses, vascular closures, and infections, occurred.[16] Although rare, their consequences are often severe and may lead to extensive interventions, including surgery. Consequently, this led to renewed interest in MC, with its known advantages: (1) nonstop observation of the puncture site until achieving full hemostasis, (2) continuous surveillance of the patient due to face-to-face contact, and (3) adaptation of compression time depending on the anticoagulants used. MC need not necessarily be done by physicians but can as well be performed by assistant personnel, as demonstrated in Great Britain.[17,18] Our present study corroborates these findings and illustrates that MC by paramedics is a safe and effective way to achieve hemostasis and can be implemented into clinical routine without endangering patients.

Our 4-level training program permitted the introduction of sheath removal by paramedics using MC without any difficulty, even though no prior experience was present in this domain. The development of the program was based on known risk factors for access site–related vascular complications. To keep it as simple as possible, just 2 different variables, sheath size and type of anticoagulation, triggered assignment to the possibly applicable sheath removal strategy. Important to the developed program was the intent of its implementation in daily clinical routine, during regular business hours. In this respect, ensuring the safety of the patients was our most important ambition, and it was achieved successfully. Furthermore, we aspired to the preservation of the established proved and tested sequences in our catheterization laboratory without exorbitant time-consuming incorporation processes. Despite initial worries regarding lack of experience, the paramedics gained confidence very fast and absorbed proportionally little time. Overall, the program resulted in a speedy integration of the paramedics into the daily routine of the catheterization laboratory. Within 3 months, the training was completed and the paramedics were able to remove all kinds of sheaths from basically all catheterization procedures. To the surprise of all, the paramedics with training undercut even physicians in the rate of complications. This may be explained by a sensed reevaluation of their work, becoming more integrated in the flow of work, and adopting more responsibility.

The study period contained only the implementation phase of the "compression-by-paramedics" project. Further development of this strategy must be observed. Acquisition of access site–associated complications took place only during the in-hospital phase. Complications occurring at a later point of time may have been overlooked.

Disclosures

The authors have no conflicts of interest to disclose.

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Validation of High-Resolution Ultrasound Measurements of Intima-Media Thickness of the Radial Artery for the Assessment of Structural Remodeling

Stegemann E*, Sansone R*, Stegemann B, Kelm M, Heiss C

Angiology. 2015 Jul;66(6):574-7

Zur Vermeidung von Blutungskomplikationen wird in der Kardiologie zunehmend die Arteria radialis als Zugangsweg im Rahmen von Herzkatheter Untersuchungen verwendet. Aufgrund des geringen Gefäßkalibers ist eine Verletzung der Intima des Gefäßes während der Untersuchung zu erwarten; entsprechende Veränderungen des Intima-Media-Komplexes wurden mittels intravaskulärem Ultraschall nachgewiesen, dieser ist jedoch zur regelmäßigen Reevaluation nicht sinnvoll einsetzbar. Vor Einsatz von hochauflösendem transkutanen Ultraschall zur Langzeitevaluation der Arteria radialis nach Herzkatheteruntersuchung wurde dieses Verfahren auf Reliabilität und Reproduzierbarkeit untersucht, welche beide ausgezeichnet sind, so dass dieses Verfahren zur Langzeituntersuchung eingesetzt werden kann.

Angiology
2015, Vol. 66(6) 574-577

DOI: 10.1177/0003319714544699
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Validation of High-Resolution Ultrasound Measurements of Intima–Media Thickness of the Radial Artery for the Assessment of Structural Remodeling

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Abstract

Radial artery (RA) intima–media thickness (IMT) could be used to study short- and long-term structural vascular adaptation following transradial cardiac catheterization. We aimed at assessing the reliability and reproducibility of RA-IMT measurement. Using high-resolution ultrasound, we studied RA-IMT in 17 patients, who underwent transradial catheterization via the right RA 1 to 12 months before. Radial artery intima–media thickness was measured in both arms, with the left RA as control. Repeated measurements were performed by 2 examiners and offline analyses were performed by independent blinded interpreters. Radial artery intima–media thickness was highly reliable with an interclass correlation coefficient (ICC) of 0.911 [0.870-0.939], a high examiner ($ICC_{examiner}$ 0.910 [0.883-0.931]), and interpreter agreement ($ICC_{interpreter}$ 0.963 [0.954-0.971]). Intima–media thickness at the radial access site was significantly increased compared with the contralateral RA (0.30 $\pm$ 0.056 vs 0.41 $\pm$ 0.055 mm, $P < .00001$). Radial artery intima–media thickness can be measured reliably using high-resolution ultrasound. Initial data suggest that transradial catheterization leads to long-term structural adaption processes.

Keywords

intima–media thickness, radial artery, reliability, reproducibility, transradial catheterization

Introduction

Arterial intimal injury leads to remodeling of the arterial wall with intimal hyperplasia and an increase in intima–media thickness (IMT). As a consequence of manipulation in smaller arteries as for catheterization procedures via the transradial approach (TRA), considerable injury is expected. Therefore, an increase in radial artery (RA) IMT (RA-IMT) after TRA was demonstrated by intravascular ultrasound.[1] Thickening of the arterial wall is associated with a persistent increase in vessel stiffness leading to long-term functional changes.[2]

The rate of IMT thickening, mainly of the carotid arteries, is used to predict overall cardiovascular risk. The measurement of RA-IMT following arterial injury after TRA could serve as a readily available indicator for the degree of damage and remodeling that can be easily captured by high-resolution ultrasound. Although reliability and reproducibility of carotid artery IMT measurements are well established,[3] this method is not established for other vessels. Therefore, we aimed at validating RA-IMT measurements by high-resolution ultrasound.

Materials and Methods

Study Design

Radial artery intima–media thickness in both RAs was measured in 17 patients who had undergone a catheterization procedure by TRA an average 6 months before. The examination was conducted by 2 examiners at 3 locations of each RA and replicated once by the first examiner. Radial artery intima–media thickness measurement was performed offline by an independent interpreter.

Measurement Protocol

Measurement of RA-IMT consisted of 2 steps, ultrasound image acquisition and image analysis. Total IMT variance

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Table 1. Patient Baseline and Procedure-Related Characteristics.

Baseline Characteristics	
Age, years	60.6 ± 10.6
Gender male, n (%)	15 (88%)
BMI, kg/m^2	26.8 ± 3.8
SBP, mm Hg	128.8 ± 14.7
DBP, mm Hg	80.9 ± 9.4
Chronic renal insufficiency, n (%)	15 (88%)
Diabetes, n (%)	3 (18%)
Current smoker, n (%)	5 (29%)
Past smoker, n (%)	12 (71%)
CHD, n (%)	11 (65%)
Medical therapy	
Aspirin, n (%)	13 (77%)
Clopidogrel, n (%)	14 (82%)
Coumadin, n (%)	1 (6%)
ACE blocker, n (%)	12 (71%)
β-blocker, n (%)	13 (77%)
Statin, n (%)	13 (77%)
Procedure-related characteristics	
Diagnostic catheterization	10 (59%)
PCI	7 (41%)
Sheath size 5F	13 (76%)
Sheath size 6F	4 (24%)
Number of catheters needed: 2	1 (6%)
Number of catheters needed: 3	8 (47%)
Number of catheters needed: 4	6 (35%)
Number of catheters needed: 5	2 (12%)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

depends on variance introduced by both steps. We, therefore, assessed reliability and agreement for both the acquisition and measurement process. Radial ultrasound acquisition was independently performed by 2 examiners and repeated twice by one of them. Image analysis and measurements were done blinded on all acquired images. Intrainterpreter reliability, interinterpreter reliability, and agreement of RA-IMT measures were estimated.

Ultrasound Equipment and Acquisition

Radial artery intima–media thickness was measured in the lying position with the forearm in supine state. A 13-MHz probe (12L-RS, GE Healthcare, Wauwatosa, Wisconin) with a 38-mm field of view connected with a Vivid i ultrasound scanner (GE Healthcare) was applied for the measurements. Both RAs were examined at the radial access site (0-5 cm) as well as 5 to 10 and 10 to 15 cm proximal to the access site.

Semiautomatic Analysis

Radial artery intima–media thickness was defined as the distance from the lumen–intima interface to the media–adventitia interface of the posterior wall.[3] The Brachial Analyzer software (Medical Imaging Applications LLC, Coralville, Iowa) was used for semiautomatic measurement of the RA-IMT.

Patient Demographics

The following patient characteristics were collected: age, weight, systolic and diastolic blood pressure, gender, kidney function, presence of diabetes, smoking status, cholesterol level, and severity of coronary heart disease. The following procedure-related characteristics were captured: type of intervention, sheath size, and the number of applied catheters.

Statistical Analyses

Data were entered and stored in a validated custom-made database. Statistical analyses were conducted using the R-Programming language.[4] Continuous variables were described as mean ± standard deviation (SD), whereas categorical variables were reported as counts and percentages. Reliability was estimated using the intraclass correlation (ICC) coefficients. The ICC (2, k) was calculated to assess the reliability for each source of variation in the measurement process.[5,6] The ICC estimate and 95% confidence intervals were obtained and reported. The R-package[4] "irr" version 0.84 (cran.r-project.org/web/packages/irr) was used for ICC calculation. Standard error of the mean (SEM) and minimal detectable difference (MDD) were calculated as an estimate of agreement for each source of variation. The SEM was calculated as SEM = SD × sqroot (1-ICC) and as MDD = 1.96 × sqroot (2) × SEM. A limits of agreements plot was prepared for each source of variation.[7,8]

Results

Baseline Demographic and Procedure-Related Characteristics of Study Population

Baseline characteristics of the study group are listed in Table 1. Almost 60% of the procedures were diagnostic catheterizations, predominantly performed with a 5F sheath and with an average number of 3.5 catheters used. All patients were smokers, and 29% of them were current smokers.

Reliability, Repeatability, and Interpreter Agreement of RA-IMT Measurement

Reliability, repeatability, and interpreter agreement of RA-IMT measurement are shown in Figures 1 to 3. The ICC for the examination showed excellent reliability with an ICC of 0.911 (0.870-0.939) and an MDD of 0.027 mm. The interpreter agreement was excellent with an ICC of 0.963 (0.954-0.971) and an MDD of 0.011 mm. Independency of the examiner could also be proven by an ICC of 0.910 (0.883-0.931) and an MDD of 0.027 mm.

Comparison of RA-IMT Measurement

At 6 (1-12) months, the RA-IMT of the RA used for the catheterization procedure was significantly increased compared with the contralateral RA (0.30 ± 0.056 vs 0.41 ± 0.055 mm, $P < .00001$) as shown in Figure 4. Radial artery intima–media thickness was similar at all sites (0-15 cm from access

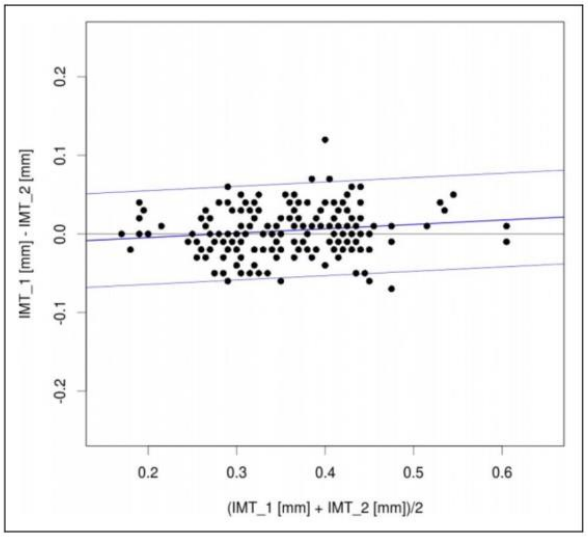

Figure 1. Bland-Altman plot for repeated IMT by the same examiner. IMT indicates intima–media thickness.

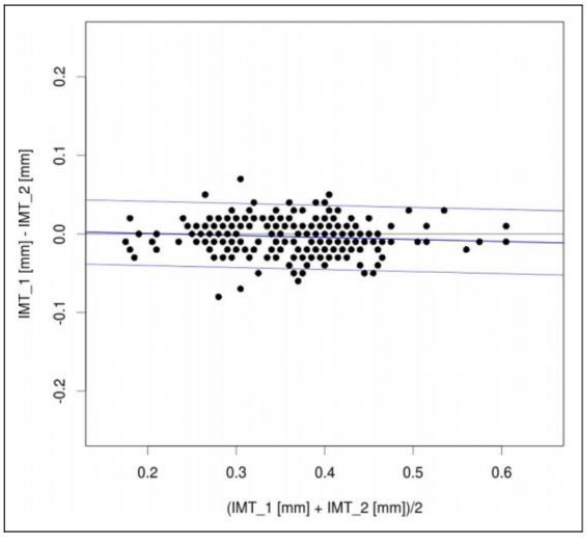

Figure 3. Bland-Altman plot for IMT by different interpreters. IMT indicates intima–media thickness.

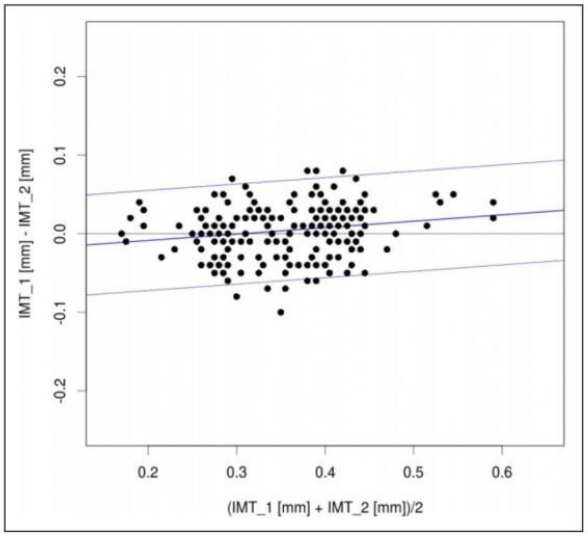

Figure 2. Bland-Altman plot for IMT by different examiners. IMT indicates intima–media thickness.

site) of the ipsilateral RA. Gender, medical treatment with statins, and blood pressure showed no influence of the extent of RA-IMT thickening. As the detection of predictors for IMT thickening was not the primary study objective, this conclusion has to be considered with care not least due to the small number of patients included.

Discussion

Our study demonstrates that the RA-IMT can be reliably and reproducibly measured via high-resolution ultrasound. Following TRA catheterization, thickening of the RA-IMT was observed.

The TRA for cardiac catheterization procedures, described decades before, has undergone a revival.[9] Low access site-related vascular bleeding rates and improved patient comfort compared with the transfemoral approach (TFA) are advantages. Proven benefits in acute ST-segment elevation myocardial infarction for the short-term outcome ended in a Class IIa recommendation of the European Society of Cardiology for the TRA provided that the procedure is performed by an experienced radial operator.[10] However, whether the proven reduction in acute bleeding complications and the reduced number of needed transfusions can impact survival is an open question.[11] Long-term benefit of TRA compared with TFA has not been shown yet,[12,13] but there are several ongoing randomized trials to answer this question.

Frequently suppressed facts in relation to the TRA are long-term changes in the RA itself and resulting consequences for the patients.

Radial arteries of patients with coronary artery disease are atherosclerotic[14] and progression of atherosclerosis, as a consequence of catheter-induced intima lesions, is probable. Transradial approach results in impaired RA function.[15] Moreover, previous puncture of the RA was shown to be related to more intimal hyperplasia and reduced early graft patency if then used for coronary artery bypass grafting.[16] In addition, occlusions of the RA are often unnoticed in the face of a patent ulnar artery and palmar arch, leading to underestimation of the real damage that TRA may cause. Uncertainty and poor specifications of long-term remodeling processes of the RA after TRA led the transradial committee of the Society for Cardiovascular Angiography and Interventions to publish the recommendation to avoid TRA if an arteriovenous shunt for dialysis is planned or the RA could be potentially used as a conduit for aortocoronary bypass.[17]

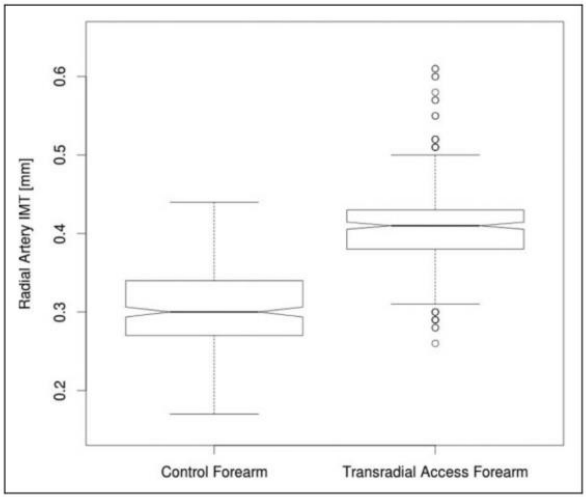

Figure 4. Intima–media thickness (IMT) of radial artery for transradial access (TRA) forearm compared to IMT of radial artery for contralateral control forearm.

Our opinion is that in a population with rising life expectancy and consequently higher rates of renal insufficiency as well as increasing cardiovascular morbidity, more information has to be gathered before adopting the TRA for all patients. Patient groups at increased risk of distinct vessel wall changes have to be identified to avoid making the RA unsuitable for further use.

Prospective studies concerning remodeling processes of the RA following catheterization procedures with TRA using the RA-IMT could be performed to assess vessel damage.

In conclusion, we report that the measurement of the RA-IMT is a practical method with excellent reliability and reproducibility allowing the evaluation of long-term changes in the RA after catheterization procedures.

Authors' Note

Emilia Stegemann and Roberto Sansone contributed equally to the manuscript. Conception and design of the study were worked out by ES, RS, BS, MK, and CH. Acquisition and interpretation of data were carried out by ES and RS; statistical analyses were performed by BS. Drafting of the article was done by ES and RS; critical revising was carried out by CH and MK. Final approval of the version to be published was obtained by ES, RS, BS, MK, and CH.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Early and late response-to-injury in patients undergoing transradial coronary angiography: arterial remodeling in smokers

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Am J Cardiovasc Dis. 2014 Jun 28;4(2):47-57

Veränderungen des Intima-Media-Komplexes sowie der Fluss-Mediierten-Dilatation (FMD) als Surrogat für die endotheliale Funktion der Arteria radialis nach Herzkatheter Untersuchungen mit transradialem Zugangsweg sind beschrieben. Rauchen ist der wichtigste modifizierbare Risikofaktor für die Entstehung kardiovaskulärer Erkrankungen und führt zu einer nachweisbaren endothelialen Dysfunktion. Untersucht wurde der Einfluss von aktivem und ehemaligem Rauchen auf die Gefäßsteifigkeit, die FMD und die Intima-Media-Dicke. Bei aktiven Rauchern zeigen sich eine verlängerte Einschränkung der endothelialen Funktion, eine erhöhte Gefäßsteifigkeit und eine verzögerte Regeneration im Vergleich zu Nichtrauchern.

Am J Cardiovasc Dis 2014;4(2):47-57
www.AJCD.us /ISSN:2160-200X/AJCD0000518

Original Article

Early and late response-to-injury in patients undergoing transradial coronary angiography: arterial remodeling in smokers

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Received April 13, 2014; Accepted April 25, 2014; Epub June 28, 2014; Published July 1, 2014

Abstract: Objectives: To investigate the effect of smoking on vascular response to transradial coronary angiography (TCA). Background: Cigarette smoking is the most important modifiable cardiovascular risk factor associated with endothelial dysfunction. Methods: Radial artery flow-mediated vasodilation (RA-FMD), local stiffness (fractional diameter change), intima-media thickness (IMT), luminal and external arterial diameter were measured in 40 current smokers (CS) and former smokers (FS) at 6-14 months at the site of previous TCA and contralateral control artery. Vascular regenerative capacity was studied as chemotactic cell migration *in vitro* and *ex vivo* (n=10) and the time course of endothelial functional recovery following RA-FMD up to 72 h after TCA (n=10). Results: At 10 ± 3 months after TCA, subjects exhibited significant local stiffening and increased IMT as compared to the control arm. These late structural changes were significantly more pronounced in CS as compared to FS. IMT thickening correlated with packyears, number of daily cigarettes, and inversely with RA-FMD. Nitric oxide synthase (NOS)-dependent chemotaxis of CS' circulating angiogenic cells was impaired. *Ex vivo* incubation of endothelial cells with CS' plasma inhibited NOS-dependent endothelial wound closure and chemotaxis. *In vivo*, TCA acutely decreased RA-FMD. At 24 h, RA-FMD had recovered in FS but remained impaired at 24 h and only recovered at 48 h in CS. Conclusion: In active smokers, transradial coronary angiography is associated with delayed early recovery from transient endothelial dysfunction, decreased NOS-dependent vascular regeneration, and late arterial remodeling pointing towards potential harmful effects of transradial coronary angiography on vascular function in distinct subsets of patients.

Keywords: Smoking, intima media thickness, transradial coronary angiography, endothelial function, prevention

Introduction

Ever since the first successful diagnostic transradial coronary catheterization (TCA) by Campeau in 1989, the radial artery (RA) approach has gained increasing acceptance and has become a standard approach in most centers. TCA was shown to be safe with lower rates of access site complications, shorter hospital stay, and improved patient comfort as compared with the transfemoral access [1]. Nevertheless, radial artery occlusions might be underestimated at discharge [2] and the injury inflicted by the radial sheath may lead to later intimal hyperplasia or even occlusion [3], potentially limiting the quality of the artery for later use as a bypass graft, or dialysis shunt. Recently, we have shown that TCA leads to an acute, yet transient, impairment of endothelium-dependent vasodilation of the radial and brachial artery [4]. Furthermore, our data suggested that the regain of vasodilator function was significantly slowed in smokers as compared to the non-smokers. It was previously shown, that active smoking and passive smoke exposure not only impairs endothelial function, but also cellular processes important for endothelial regeneration and maintenance. *In vitro*, cigarette smoke causes generation of reactive oxygen species, impairs nitric oxide (NO) production, and causes apoptosis and activation of endothelial cells, all of which may contribute to the vascular toxicity of cigarette smoke [5]. We have shown that even plasma taken from

non-smokers who were briefly exposed to second hand smoke blunts eNOS-dependent chemotaxis in circulating angiogenic cells (CACs) and endothelial cells [6]. However, whether smoking in the context of a defined mechanical injury to the RA during TCA negatively affects the homeostatic repair processes necessary to inhibit long term consequences by means of structural vascular remodeling is unclear.

Therefore, the aim of the study was to investigate the effect of current smoking on the late arterial remodeling in response to injury of the RA during TCA. To investigate the impact of smoking status on early regenerative response, we performed cell migration experiments *in vitro* and *ex vivo* and followed the early recovery of endothelial function.

Materials and methods

Study population

In a first series (Series 1) we recruited patients, that had undergone first time elective TCA with a transradial access at 6-14 months prior to screening date that were current smokers (CS, n=17) or former smokers (FS, n=23) as defined by smoking abstinence of >1 year prior to TCA. In this group, late arterial remodeling was studied. In a second (Series 2(a), n=10) and third series (Series 2(b), n=10), we recruited CS and FS that were scheduled for first time elective cardiac catheterization. Blood was drawn from subjects in series 2(a) to study regenerative processes *in vitro* and *ex vivo*. The time course of endothelial functional recovery was studied in series 2(b). See **Figure 1** for study flow.

Inclusion criteria were the indication for a TCA by a cardiologist and a positive smoking history. Patients were excluded from the study, if they had undergone previous radial cannulations or had an abnormal Allen test consistent with insufficient ulnar collateral supply. Other exclusion criteria were acute inflammation (C-reactive protein >0.5 mg/dl), malignancies, heart rhythm other than sinus rhythm, and heart failure New York Heart Association functional class III to IV, and terminal renal failure. CAD patients were on standard optimal medical therapy with statin, beta-blocker, ACE-inhibitor, aspirin, or clopidogrel. The study protocol was approved by the ethics committee of the Heinrich Heine University Duesseldorf.

Study protocol

Series 1 – Late arterial remodeling: In a first series (total n=40, CS n=17, FS n=23), we investigated late arterial structural remodeling as fractional diameter change (FDC), intima-media thickness (IMT), luminal and external arterial diameter, and radial artery endothelial function by flow-mediated vasodilation (RA-FMD) in patients that had undergone first TCA at 6-14 month prior to inclusion. Vascular ultrasound exams included measurements of the cannulated radial artery in CS and FS (inter-individual control) and of the contralateral control arm without an intervention (intra-individual control).

Series 2 – (a) In vitro/ex vivo regenerative capacity: In a second group of CS (n=5) and FS (n=5), we quantitated the number of CACs in circulating blood and determined the migratory capacity after *ex vivo* culture and collected plasma. We tested the impact of the plasma on endothelial wound closure and endothelial cells migratory capacity *ex vivo*.

(b) Early recovery of endothelial function: We studied in a third series of CS (n=5) and FS (n=5) the early time course of RA-FMD at -1 h (baseline) up to 72 h after TCA.

Ultrasound measurements of RA-FMD, arterial diameters, IMT, and FDC

FMD was measured as previously described [6]. Briefly, the diameter and flow velocity of the RA was measured using a 12 MHz transducer (Vivid I, GE) and automatic edge-detection software (Brachial Analyzer, Medical Imaging Applications, Iowa City, Iowa) yielding standard deviations of mean differences between repeated measurements of less than 1%. Reactive hyperemia was induced by 5 min of lower arm occlusion with a sphygmomanometric cuff inflated to 200 mmHg. After cuff deflation, 20, 40, 60, and 80 sec, the diameter was assessed and FMD calculated as maximal relative diameter gain relative to baseline. External diameters reflected the media adventitia interface. Internal/luminal arterial diameters were calculated as diastolic external diameter-(2*IMT). IMT was measured with an automatic contour detection software between the intimal and adventitial layers (Vivid I, GE) at identical sites used for RA-FMD measurements. Local

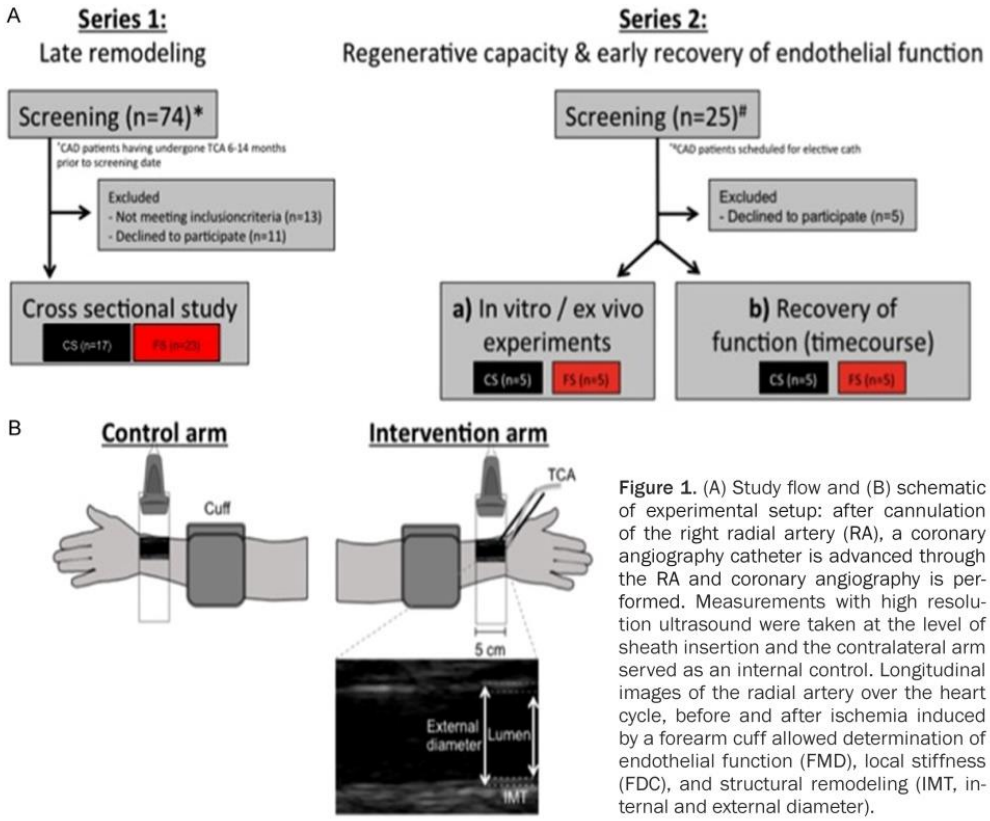

Figure 1. (A) Study flow and (B) schematic of experimental setup: after cannulation of the right radial artery (RA), a coronary angiography catheter is advanced through the RA and coronary angiography is performed. Measurements with high resolution ultrasound were taken at the level of sheath insertion and the contralateral arm served as an internal control. Longitudinal images of the radial artery over the heart cycle, before and after ischemia induced by a forearm cuff allowed determination of endothelial function (FMD), local stiffness (FDC), and structural remodeling (IMT, internal and external diameter).

arterial stiffness was determined at the site of RA-FMD measurements as a fractional diameter change (FDC) during the heart cycle and calculated as $diameter_{systolic}$-$diameter_{diastolic}$/$diameter_{diastolic}$.

Endothelial cell and CAC experiments

In a subgroup of CS and FS (Series 2(a), n=10), CAC numbers and functional activity were determined in venous blood samples taken into heparinized vacutainer tubes (R&D) from a cubital vein at hospital admission before TCA. CAC number in whole blood was measured by flow-cytometry as CD34/KDR double-positive cells in the lympho-mononuclear cell gate [6, 7]. Functional CAC characterization was performed after *ex vivo* expansion. Peripheral blood mononuclear cells (PBMCs) were isolated based on the Ficoll method (Vacutainer CPT, Becton Dickinson, Franklin Lakes, NJ) and cultured for 7 days on fibronectin-coated plates. To confirm the endothelial phenotype and survival, we performed fluorescent staining to detect lectin-binding and acLDL-uptake. Chemotaxis towards a VEGF gradient (Sigma, 50 ng/ml in EBM-2, 0.5% BSA) was quantified using a modified Boyden chamber. CACs were plated in the upper of two chambers (Corning Transwell) and number of migrated cells counted on the lower side of the dividing membrane after 6 h.

To test whether CS plasma inhibited regenerative capacity of endothelial cells, plasma was obtained from venous blood of CS and FS. Scratch assays and cell migration assays were performed with HUVECs (Lonza, cultured to maximum of passage 3) incubated with (a) basal cell medium, (b) plasma of CS, and (c) FS. Cell migration was quantified by a transwell chemotaxis assay using a modified Boyden chamber. Migration of both CACs and HUVECs was measured as follows: cells ($2*10^4$) were

Table 1. Clinical and procedural characteristics of study population; series 1: Late remodeling (mean ± SD)

A.	Subject characteristics	CS	FS	*p*
	n (male/female)	17/0	21/2	
	Age (yrs)	58 ± 11	60 ± 10	*0.545*
	CAD (1, 2, 3)	11/2/6	14/3/7	
	PAD	0	0	
	Carotid disease	0	0	
	BMI (kg/m^2)	27 ± 2	27 ± 3	*0.493*
	GFR (ml/min)	79 ± 18	79 ± 15	*0.946*
	CRP (mg/dl)	0.3 ± 0.6	0.3 ± 0.4	*0.765*
	HR (bpm)	66 ± 7	68 ± 6	*0.271*
	SBP (mmHg)	132 ± 8	129 ± 12	*0.332*
	DBP (mmHg)	83 ± 9	82 ± 7	0.675
	Packyears (n)	44 ± 20	32 ± 20	*0.057*
	HbA1c	5.9 ± 0.6	5.7 ± 1.3	*0.592*
	Total cholesterol (mg/dl)	202 ± 37	197 ± 25	*0.649*
	LDL (mg/dl)	136 ± 38	136 ± 15	*0.990*
	HDL (mg/dl)	48 ± 5	49 ± 4	*0.839*
	Beta-blocker (%)	100	82	
	Statin (%)	90	82	
	ACEI/ARB (%)	90	94	
	Clopidogrel (%)	90	53	
	Aspirin (%)	100	92	
B.	Procedural characteristics	CS	FS	*p*
	Time after TCA (months)	10 ± 6	10 ± 6	*0.868*
	Elective TCA (%)	100	100	
	Stable CAD (%)	100	100	
	NSTEMI/STEMI (%)	0	0	
	5F sheath (%)	76	74	
	6F sheath (%)	24	26	
	Irradiation time (min)	11 ± 14	10 ± 10	*0.750*
	Contrast volume (ml)	53 ± 40	54 ± 34	0.940
	Dose-area product (mGy*cm^2)	3,601 ± 3,569	3,485 ± 2,489	*0.916*
	Number of catheters (n)	3.7 ± 0.8	3.3 ± 0.6	*0.442*
	Heparin (U/l)	3,700 ± 1,100	3,480 ± 940	*0.880*
	PCI (%)	33	22	
	$GP_{IIaIIIb}$-inhibitor (%)	6%	4%	

plated in EBM-2 medium (without other supplements, containing 63 mg/l L-arginine) after supplementation of (a) either 0.5% BSA, (b) 10% plasma from smokers (containing approximately 5% albumin), and (c) 10% plasma from non-smokers in the upper of 2 chambers divided by a membrane with 8-µm pores (Corning Transwell). We tested the chemotactic properties of vascular endothelial growth factor (VEGF, Sigma) at 50 ng/ml added to the lower chamber; the NOS inhibitor NG-nitro-L-arginine (100 µmol/l) was added to both the upper and lower chamber: The number of migrated cells was determined on 5 random 100x optical fields per membrane after 6h incubation. To distinguish the effects on chemokinetic from chemotactic capacity, BSA or plasma were added to upper and lower chambers. Scratch assays were performed in confluent HUVECs on fibronectin coated cell culture slides (Chambertech). A pipette tip was used to induce a scratch. Closure of the endothelial wound was evaluated until completion by blinded investigators in hourly intervals using an inverted microscope.

Statistical analyses

Results are expressed as means ± standard deviation (SD). Comparisons between groups were analyzed by ANOVA (gateway test) and, if significant, consecutive post-hoc test (Bonferroni) performed. Intra-individual comparisons were analyzed using repeated measurements ANOVA. Linear relationships between continuous variables were expressed as Pearson's r. Statistical significance was assumed at $p \leq 0.05$. All statistical analyses were performed using PASW Statistics 18.

Results

Baseline characteristics

See **Table 1** for clinical and procedural characteristics of series 1. (Characteristics of series 2 subjects supplied as Supplemental Tables 1 and 2) Between FS (black) and CS (red), there were no significant differences in age, presence of 1, 2, or 3-vessel coronary-artery-disease, blood pressure, and cholesterol, CRP, glomerular filtration rate (GFR), and fasting glucose levels. Packyears were significantly lower

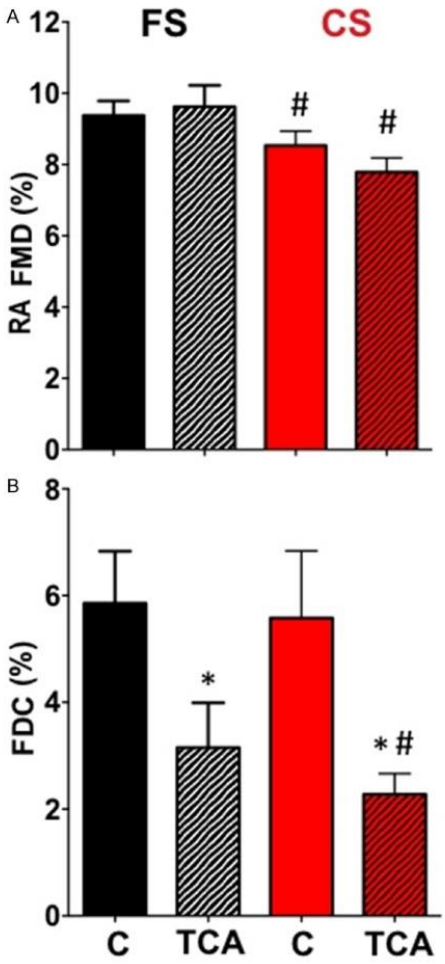

Figure 2. Endothelial function and late local arterial stiffness following TCA. Radial artery (A) flow-mediated dilation (FMD) and (B) FDC were measured 10 months after a transradial catheterization (TCA) in the interventional arm and the contralateral control arm in current smokers (CS, red) and former smokers (FS, black). *p<0.05 vs *control arm* #p<0.05 vs. *FS* (n=40). "C" denominates control arm and "TCA" the arm which was used as access site for TCA.

in the FS (34.0 ± 5.1) as compared to the CS (54.3 ± 6.4, *p=0.012*). Cotinine levels were significantly lower in FS confirming current non-smoking status. The procedural characteristics did not differ between CS and FS.

Current smoking promotes structural remodeling of the RA following TCA

We investigated the RA at the area of the sheath insertion for the TCA and contralateral control arm at 10 ± 3 months after subjects had undergone their first TCA (**Figure 1B**). RA-FMD was significantly lower in CS as compared to FS (**Figure 2**); no significant differences were found between the TCA and control arm. FDC was decreased in the TCA arm of both CS and FS as compared to control arm suggesting increased local stiffness due to TCA. However, the FDC was significantly lowered in CS as compared to FS suggesting more pronounced local arterial stiffening due to smoking status (4.0 ± 1.2% vs. 1.2 ± 0.9%, *p=0.003 vs. FS*). We observed that IMT was significantly increased in both CS and FS as compared to the respective non-cannulated contralateral control arm (**Figure 3**). IMT in the TCA arm of CS was significantly greater as compared to FS (0.44 ± 0.07 mm vs. 0.37 ± 0.05 mm, *p=0.001 vs FS*). The IMT on the control arm was not significantly different between CS and FS (0.32 ± 0.06 mm vs. 0.31 ± 0.05 mm, *p=0.726 vs FS*). Intimal thickening (Delta TCA and control arm) was approximately doubled in CS (IMT_{Delta} CS: 0.096 ± 0.088 mm, FS: 0.053 ± 0.058 mm, *p=0.04*). Furthermore, we detected a significant increase of RA external diameter in CS following TCA (2.97 ± 0.30 mm vs. 2.71 ± 0.39 mm, *p=0.027 vs. FS*). The RA luminal diameter did not differ significantly in the interventional arms (2.03 ± 0.37 mm vs. 2.01 ± 0.33 mm, *p=0.81 vs. FS*). On the contralateral control arm, no significant differences in the external (2.73 ± 0.33 mm vs. 2.72 ± 0.35 mm, *p=0.96 vs. FS*) and luminal diameter (2.10 ± 0.37 mm vs. 2.12 ± 0.35 mm, *p=0.82 vs. FS*) were detected.

Univariate correlations were found between IMT and packyears (r=0.57, p=0.002) and daily cigarette consumption (r=0.7, p=0.001, **Figure 4**). Furthermore, a negative univariate correlation existed between IMT and FMD (r=-0.44, p=0.041, n=40) in the intervention arm.

Impairment of in vitro and ex vivo regenerative capacity in CS

We observed significantly lower numbers of CD34/KDR (FS: 0.42 ± 0.19%PBMNC, CS: 0.07 ± 0.06%PBMNC, *p=0.04*) in CS as compared to FS. We tested the migratory capacity of CACs cultured from CS and FS blood (**Figure 5**). Although CACs of CS exhibited similar random cell movement (chemokinesis) as compared to FS CACs, these cells exhibited practically abol-

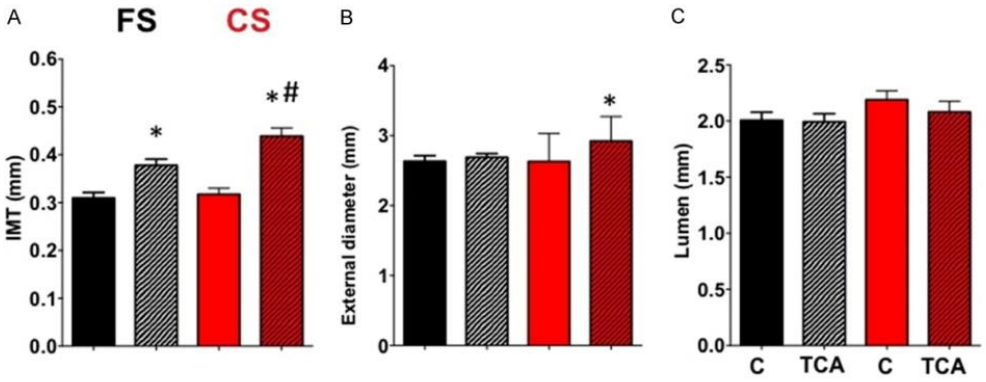

Figure 3. Late arterial remodeling of radial artery following TCA. (A) IMT, (B) external diameter, and (C) lumen were measured 6-14 month after a transradial catheterization (TCA) at the interventional arm and at the contralateral control arm in current smokers (CS, red) and former smokers (FS, black). CS exhibited significantly greater external diameter due to greater intima media thickness (IMT) as compared to FS and control arm (C). *p<0.05 vs. *control arm* #p<0.05 vs. *FS*. "C" denominates control arm and "TCA" the arm which was used as access site for TCA.

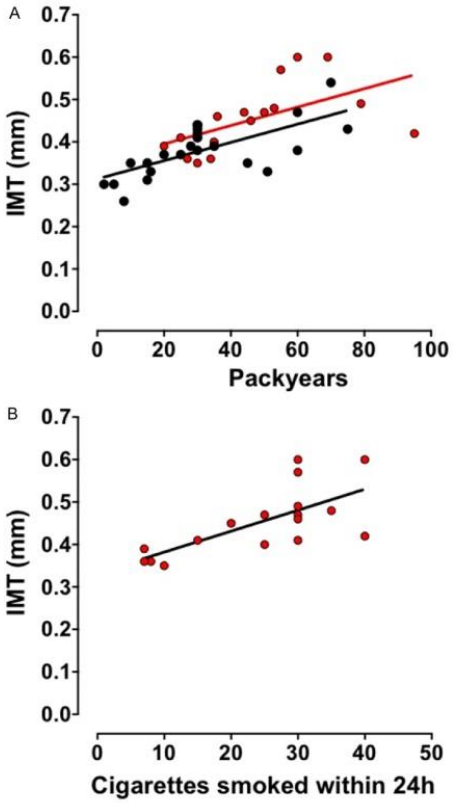

Figure 4. Correlation of IMT and smoking: (A) Packyears and IMT in CS (r=0.57, p<0.002, n=17) and in FS (r=0.63, p<0.001, n=23) and (B) IMT and the number of cigarettes consumed daily in CS (r=0.7, p<0.001, n=17).

ished chemotaxis i.e. CACs did not migrate towards a VEGF cytokine gradient. FS CAC chemotaxis was inhibited by L-NMMA confirming that NOS activity was required to allow chemotaxis [6, 8]. L-NMMA did not affect chemotaxis in CS suggesting that CS CACs had lost NOS activity. Similar results with impaired NOS dependent chemotaxis were seen in the second series of experiments in which endothelial cells (HUVEC) were incubated with CS and FS plasma. Furthermore, plasma isolated from CS impaired endothelial wound healing. Incubation with CS plasma almost doubled wound closure time similar to prolonged closure times that we observed in the presence of NOS inhibitor L-NMMA.

Current smoking delays early recovery of vasodilator dysfunction

CS exhibited significantly lower RA-FMD at baseline (7.3 ± 1.0% vs. 9.5 ± 0.7%, *p=0.004,* **Figure 6**). At 6 h after TCA, RA-FMD values decreased significantly in both groups (4.1 ± 0.7% vs. 4.7 ± 1.2%, *p=0.912 between groups*). Whereas in FS RA-FMD had returned to baseline at 24 h (9.1 ± 1.3%, *p=0.465 vs. baseline*), CS remained impaired at 24 h (5.3 ± 0.7%, *p=0.043 vs. baseline*) and recovered at 48 h (7.0 ± 0.7%, *p=0.712 vs. baseline*). To determine the contribution of endothelium-dependent vasomotor dysfunction to the impairment of FMD after catheterization, we measured the endothelium-independent smooth muscle response to oral GTN after FMD measurements.

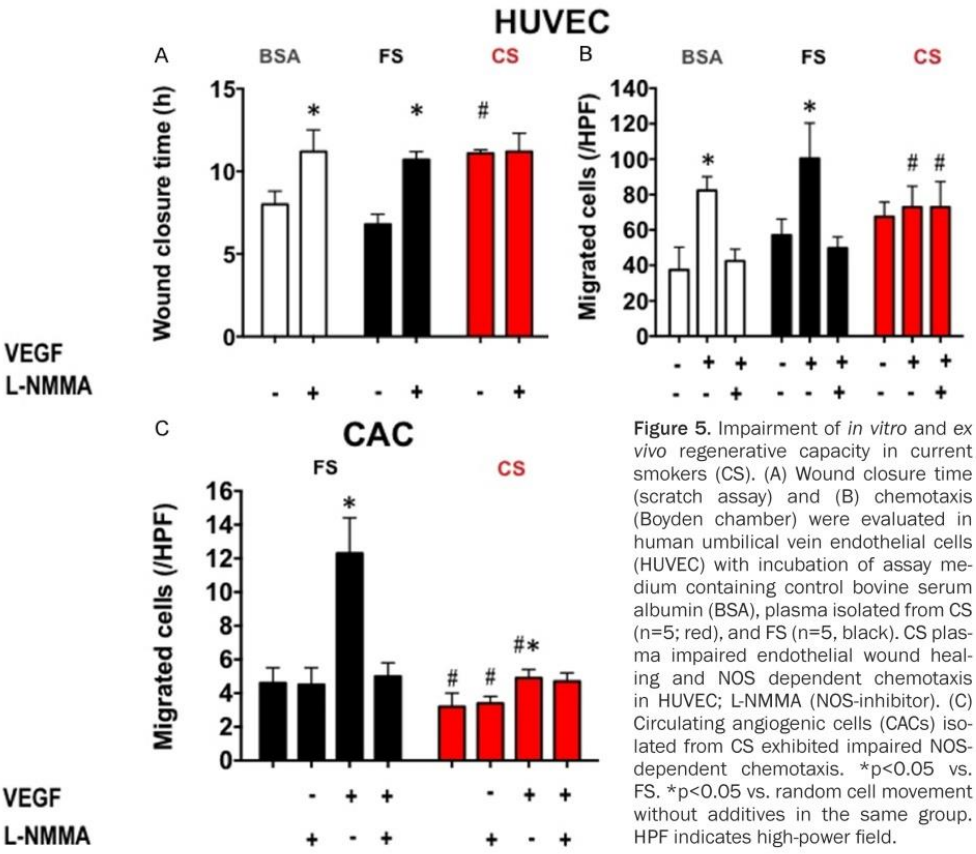

Figure 5. Impairment of *in vitro* and *ex vivo* regenerative capacity in current smokers (CS). (A) Wound closure time (scratch assay) and (B) chemotaxis (Boyden chamber) were evaluated in human umbilical vein endothelial cells (HUVEC) with incubation of assay medium containing control bovine serum albumin (BSA), plasma isolated from CS (n=5; red), and FS (n=5, black). CS plasma impaired endothelial wound healing and NOS dependent chemotaxis in HUVEC; L-NMMA (NOS-inhibitor). (C) Circulating angiogenic cells (CACs) isolated from CS exhibited impaired NOS-dependent chemotaxis. *p<0.05 vs. FS. *p<0.05 vs. random cell movement without additives in the same group. HPF indicates high-power field.

Our results show that the GTN response was not significantly different between CS and FS at baseline (13.4 ± 0.5% vs. 14.1 ± 0.7%, *p=0.116 between groups*) and all consecutive time points suggesting that smoking status did not influence smooth muscle function and that the degree of mechanical injury was comparable between groups. GTN significantly decreased in both groups at 6 h (7.4 ± 2.0% vs. 7.1 ± 0.6%, *p=0.787 between groups)*, remained decreased at 24 h (10.1 ± 0.8% vs. 10.7 ± 1.7%, *p=0.541 between groups)*, and returned to baseline values at 48 h (13.2 ± 1.1% vs. 14.4 ± 1.4%, *p=0.154 between groups)*. Measurements at the control arm remained unaffected.

Discussion

Smoking leads to endothelial dysfunction promoting structural remodeling

We [4] and others [9] have previously shown that active cigarette smoking and even exposure to secondhand smoke [6] leads to acute impairment of endothelial function and might also have a longer-lasting effects by negatively impacting vascular repair mechanisms, including the migratory function of endothelial cells. Endothelial dysfunction is a major mechanism by which cigarette smoking promotes atherosclerosis [10, 11]. In the context of the present study, we showed that in current smokers the recovery of endothelial function was slower and the increase of IMT secondary to mechanical vascular irritation was more severe as compared to former smokers. In animal models, denudation of arteries leads to intima hyperplasia that is enhanced by exposure to cardiovascular risk factors [12]. Several studies demonstrated correlations with cardiovascular risk factors, including aging, systolic blood pressure [13], hypercholesterolemia [14], glucose level [15], and smoking status with impaired endothelial function. But also structural changes as measured by IMT are strongly associated with

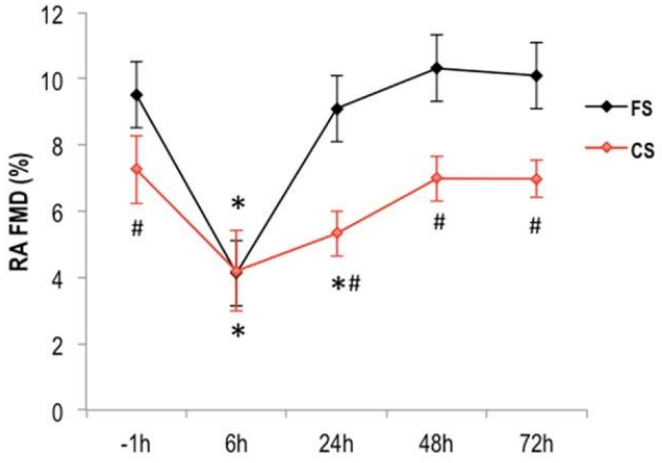

Figure 6. Early recovery of transient endothelial dysfunction after TCA (n=10). Endothelial function measured as FMD at baseline before (-1 h), after 6, 24, 48, and 72 h in current smokers (CS) and former smokers (FS) undergoing TCA. Data are presented for the radial artery FMD on the interventional arm. *p<0.05 vs. *baseline (-1 h)*, #p<0.05 vs. *FS*.

these cardiovascular risk factors. IMT is associated with the degree of impaired endothelial vasomotor function, is preceded by endothelial dysfunction, affected by treatments that improve endothelial function, and, therefore, believed to represent a long term sequel of endothelial dysfunction in a broader sense [16-18].

In 1987 Glagov et al. [19] described that during atherogenesis there is an initial intimal proliferative adaptive response, which is associated with an increased wall stress, triggering intimal hyperplasia. During this process, intimal hyperplasia temporarily stabilizes wall stress leading to gradual artery enlargement, which can be interpreted as a compensatory enlargement, i.e. positive remodeling. At some point, external arterial enlargement can no longer compensate for intimal hyperplasia and the lumen diameter starts to decrease, resulting in lumen loss/stenosis and flow restriction, i.e. negative remodeling. However, these findings are based on coronary arteries that are known to be prone to atherosclerosis. Nevertheless, we propose that a similar process can takes place in vessels, which are typically not affected to a similar extent of atherosclerosis i.e. the radial artery. Interestingly, our data show enhanced IMT thickening and compensatory external arterial diameter enlargement in current smokers, while maintaining luminal diameter reminiscent of positive remodeling as described above. A potential mechanism by which smoking might fire this process is a stimulation of smooth muscle cell-proliferation and intimal hyperplasia [20]. Several studies suggest that nicotine induced vascular smooth muscle cell proliferation, promotes atherosclerosis [21], and exaggerates post-injury neointima hyperplasia in animal models [22].

Vascular injury and long-term consequences

Our data support that arterial injury induced by arterial cannulation and sheath placement leading to endothelial denudation can be a trigger for adverse structural remodeling of the radial artery. Depending on the size of the sheath in relation to the arterial luminal diameter acute vascular dysfunction is followed by intimal hyperplasia and lumen loss. Patients with repeated transradial catheterization, showed a stronger intimal thickening and luminal loss of the RA [23]. Abe and colleagues [24] showed that placement of a 6F system during transradial interventions resulted in a decreased RA diameter at 3 month follow-up. Furthermore, Uhlemann et al. demonstrated that the use of 5F sheaths for transradial access significantly decreased the rate of radial arterial occlusion by 55%, compared with 6F sheaths [2]. These data are supported by intravascular ultrasound results of Wakeyama et al. who showed a reduced lumen diameter due to intima-media-thickening after transradial intervention with 6F sheaths and that repeated access enhanced this [23]. This structural remodeling response in particular with small sheath size might have been overlooked in other studies, as many studies investigated remodeling with angiographic techniques were only lumen diameters are investigated. Using ultrasound, we were able to detect not only the luminal diameter, but also the external diameter of the RA. Importantly, we detected that intimal hyperplasia occurred in all patients with the degree of IMT thickening and adaptive arterial enlarge-

ment inversely associated with endothelial function and the degree of cigarette smoke exposure, a known endothelial toxin. Our data suggest that patients with endothelial dysfunction are at increased risk for adverse remodeling in response to (iatrogenic) arterial injury. However, longitudinal studies in larger patient groups over longer timeframes are necessary to identify determinants of adverse remodeling and vascular complications and evaluate whether the observed changes are potentially reversible.

Smoking impairs vascular regeneration

Our current data suggest that a prolonged period of endothelial dysfunction following TCA may contribute to a more pronounced IMT thickening. Endothelial dysfunction is considered as a key factor in the pathogenesis of atherosclerosis [25]. After endothelial injury, surrounding endothelial cells migrate into the denuded area, circulating angiogenic cells home to denuded areas and can help inhibiting intimal hyperplasia. eNOS plays an integral regulatory role in vascular biology, regeneration of endothelium, and CAC function and there is ample evidence that smoking leads to dysfunction of NOS [5, 11, 26]. We here show that smokers CACs exhibited similar random cell movement (chemokinesis) as compared to non smokers' CACs. Mechanistically, we show *in vitro* that CACs chemotaxis in FS was inhibited by L-NMMA confirming that NOS activity is required to allow chemotaxis [6, 8]. L-NMMA did not affect chemotaxis in CS suggesting that CACs from CS had lost NOS activity. Incubation of human umbilical vein endothelial cells with cigarette smokers plasma led to a blockade of the endothelial nitric oxide synthase (eNOS)/NO pathway and impaired VEGF- induced migration. This suggests that the mechanisms involved in smoke toxicity are similar in endothelial cells. Several studies suggested that an impairment of vascular NO availability might contribute to an accelerated intimal hyperplasia. Yoko et al. demonstrated in eNOS-KO mice a significantly enhanced neointimal formation after balloon injury [27]. Another study demonstrated that after mechanical expansion of the femoral artery resulted in rapid onset of apoptosis of medial smooth muscle cells and enlargement of the artery [28]. Also in humans, several studies have reported remodeling processes under different clinical conditions as a dynamic phenomenon that takes place alongside atherosclerotic plaque development [23, 29, 30]. This is important because a number of risk factors, in particular smoking, promote atherosclerosis, impairs regeneration [8] and moreover current smoking inhibits the NO production [31]. The NO signaling is coupled with the ability of CACs to migrate towards VEGF [8, 32]. Our current data support, that this key NOS-dependent endothelial repair mechanism is counteracted by current smoking leading to an impaired migration in smokers and potentially facilitates late intima-hyperplasia following arterial injury in active smokers. This is supported by our correlations between IMT and parameters of current smoking. In addition, pathophysiological studies addressing smoking and wound healing suggest a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complications [33]. Our data support these findings. Incubation of cells with smokers' plasma almost doubled wound closure time similar to NOS inhibitor L-NMMA, which underlines the impaired endothelial wound healing in smokers and a NOS dependent effect. Smoking cessation restores endothelium-dependent relaxations by increased release or bioavailability of NO from endothelial cells and might support wound healing effects. It is tempting to hypothesize that peri-interventional smoking cessation can help to curb vascular remodeling after TCA and thereby prevent long-term complications of this procedure and preserve the option to use the radial artery as a bypass graft or dialysis shunt. This however needs to be shown in future studies.

Conclusion

Our data suggest that current smoking status strongly impacts on the early recovery of endothelial function and structural maintenance of arteries following arterial injury during transradial coronary angiography interfering with NOS-dependent vascular repair mechanisms.

These data raise the question, whether or not active smokers should be subjected to coronary angiography via the transradial access route. Longitudinal longer term follow up studies in larger cohorts of active smokers are mandatory. Furthermore, the use, quality, and outcome of a radial artery bypass graft for CABG procedures, which might be accompanied also

by mechanical stress during harvesting of the artery, deserves further studies, at least in active smokers. The widespread use of transradial coronary angiography might be questionable in specific subsets of patients.

Acknowledgements

CH received research funding from the Forschungskommission of the Heinrich-Heine University, Duesseldorf. MK was supported by the Deutsche Forschungsgemeinschaft (DFG) (Ke405/5-1).

Disclosure of conflict of interest

None.

Abbreviations

BA, brachial artery; CAC, circulating angiogentic cells; CAD, coronary artery disease; CS, current smokers; FDC, fractional diameter change; FS, former smokers; IMT, intima-media thickness; RA, radial artery; RA-FMD, radial artery flow-mediated vasodilation; TCA, transradial coronary angiography.

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Supplemental Table 1. Characteristics of study subject; Series 2(a): Regenerative capacity

Subject characteristics	CS	FS	p
n (male/female)	5/0	5/0	
Age (yrs)	57 ± 4	59 ± 6	0.595
CAD (1, 2, 3)	3/2/0	3/2/0	
PAD	0	0	
BMI (kg/m^2)	26 ± 4	27 ± 3	0.614
GFR (ml/min)	68 ± 10	68 ± 11	0.954
CRP (mg/dl)	0.3 ± 0.1	0.3 ± 0.2	0.765
HR (bpm)	61 ± 7	67 ± 16	0.502
SBP (mmHg)	125 ± 16	130 ± 11	0.596
DBP (mmHg)	76 ± 11	78 ± 5	0.637
Packyears (n)	36 ± 8	39 ± 6	0.615
Fasting glucose (mg/dl)	92 ± 11	102 ± 18	0.352
Total cholesterol (mg/dl)	169 ± 22	164 ± 26	0.742
LDL (mg/dl)	103 ± 32	102 ± 22	0.956
HDL (mg/dl)	51 ± 17	46 ± 12	0.645
Beta-blocker (%)	100	80	
Statin (%)	100	100	
ACEI/ARB (%)	80	100	
Clopidogrel (%)	100	100	
Aspirin (%)	100	100	

In vitro and *ex vivo* experiments were performed with CACs and plasma obtained from these subjects.

1

Supplemental Table 2. (A) Subject and (B) procedural characteristics; Series 2(b): Early recovery of endothelial function

A.	Subject characteristics	CS	FS	p
	n (male/female)	5/0	5/0	
	Age (yrs)	64 ± 11	62 ± 7	0.819
	CAD (1, 2, 3)	2/2/1	3/2/0	
	PAD	0	0	
	BMI (kg/m^2)	27 ± 2	28 ± 1	0.493
	GFR (ml/min)	79 ± 18	79 ± 15	0.946
	CRP (mg/dl)	0.3 ± 0.2	0.3 ± 0.2	1.000
	HR (bpm)	64 ± 7	66 ± 7	0.797
	SBP (mmHg)	134 ± 6	128 ± 6	0.180
	DBP (mmHg)	84 ± 6	83 ± 5	0.778
	Packyears (n)	35 ± 9	48 ± 12	0.090
	Fasting glucose (mg/dl)	86 ± 10	81 ± 10	0.504
	Total cholesterol (mg/dl)	179 ± 11	176 ± 22	0.807
	LDL (mg/dl)	129 ± 13	121 ± 24	0.534
	HDL (mg/dl)	46 ± 5	50 ± 8	0.365
	Beta-blocker (%)	80	80	
	Statin (%)	100	100	
	ACEI/ARB (%)	80	100	
	Clopidogrel (%)	100	100	
	Aspirin (%)	100	100	
B.	Procedural characteristics	CS	FS	p
	Elective TCA (%)	100	100	
	Stable CAD (%)	100	100	
	NSTEMI/STEMI (%)	0	0	
	5 F sheath (%)	100	100	
	Irradiation time (min)	10 ± 12	9 ± 12	n.s.
	Contrast volume (ml)	58 ± 36	60 ± 41	n.s.
	Number of catheters (n)	3.0 ± 0.7	3.2 ± 0.8	0.694
	Heparin (U/l)	1600 ± 1140	1400 ± 1140	0.789
	PCI (%)	0	0	

2

Carbondioxide-Aided Angiography Decreases Contrast Volume and Preserves Kidney Function in Peripheral Vascular Interventions

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Angiology. 2016 Oct;67(9):875-81

Chronische Niereninsuffizienz ist eine häufige Begleiterkrankung bei Patienten mit peripherer arterieller Verschlusserkrankung. Als Alternative zu herkömmlichem Kontrastmittel kann Kohlendioxid eingesetzt werden, welches jedoch zu höherer Strahlenbelastung, schlechteren Resultaten aufgrund der nicht optimalen Bildqualität und verlängerten Untersuchungszeiten führen soll. Untersucht wurde der Einsatz von Kohlendioxid als Kontrastmittel bei Patienten mit Niereninsuffizienz, weder technischer Erfolg noch Strahlenbelastung oder Untersuchungszeit unterschieden sich signifikant. Das Auftreten kontrastmittelinduzierten Nierenversagens war unter Einsatz von Kohlendioxid signifikant geringer als bei Verwendung eines herkömmlichen Kontrastmittels, so dass ein Einsatz zur Vermeidung einer weiteren Verschlechterung der Nierenfunktion sicher und ohne Nachteile erfolgen kann.

Angiology
1-7

DOI: 10.1177/0003319715614701
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Carbondioxide-Aided Angiography Decreases Contrast Volume and Preserves Kidney Function in Peripheral Vascular Interventions

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Abstract

Chronic kidney disease is a common comorbidity in patients with peripheral artery disease. We investigated the safety and efficacy of carbon dioxide (CO_2) as supplemental contrast agent to decrease contrast volume during fluoroscopy-guided peripheral vascular procedures in routine angiological practice. We analyzed 191 consecutive interventions of the lower extremity in claudicants and critical limb ischemia (CLI) that were performed with iodinated contrast media (ICM) alone (n = 154) or with the aided or exclusive use of CO_2 (n = 37). The technical success rate, total irradiation, and intervention time were not significantly different between ICM and CO_2. No severe procedure-related complications occurred. The contrast volume was lower in CO_2 than in ICM. Although kidney function, creatinine, and estimated glomerular filtration rate was lower in CO_2 at baseline, the incidence of contrast-induced nephropathy was lower in CO_2 compared to ICM. These data support CO_2 as an alternative supplemental contrast agent that can be applied safely and efficiently to lower contrast volume during peripheral vascular interventions preventing kidney dysfunction even in patients with disease of the popliteal artery and below the knee and CLI.

Keywords

angioplasty, peripheral artery disease, contrast-induced nephropathy, carbon dioxide

Introduction

Atherosclerotic peripheral arterial disease (PAD) is a major public health burden that affects more than 27 million people across Europe and Northern America, equating to 16% of the population older than 55 years.[1] The prevalence of PAD, especially of critical limb ischemia (CLI), is rising worldwide with considerable impact on the health care and socioeconomic systems. In Germany, the number of hospital admissions of individuals with PAD increased between 2005 and 2009 by >20%.[2] In parallel, endovascular revascularization increased by 46%. Chronic renal failure, diabetes, and heart failure are common comorbidities present in almost 37%, 39%, and 15% of patients admitted with PAD, in particular those with CLI.[2]

Current guidelines recommend an "endovascular first" strategy in case of indication for revascularization.[3] The standard approach for endovascular interventions requires conventional radio opaque iodinated contrast media (ICM) for the procedures (acquisition of diagnostic images, wire guidance, and stent placement). Contrast-induced nephropathy (CIN) is a common complication in particular in patients with preexisting chronic renal disease, diabetes, heart failure, and dehydration associated with increased in-hospital and long-term mortality, respectively.[4,5] Approaches to lower the risk of CIN include cessation of concomitant nephrotoxic medication, hydration, statins, and limiting the amount of contrast medium. Besides conventional nephrotoxic contrast medium, carbon

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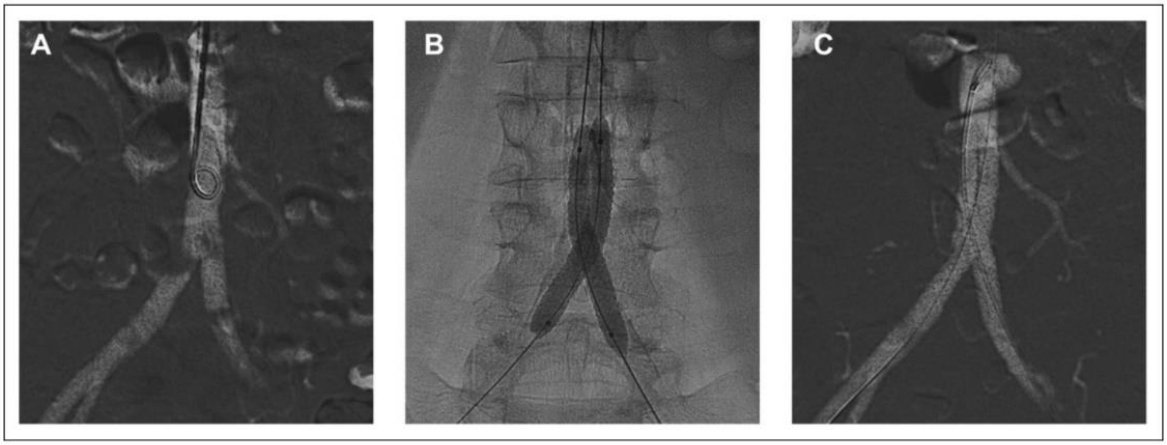

Figure 1. Example images of an exclusively CO_2-guided intervention of bilateral common iliac stenosis. A, Baseline CO_2 angiography via pigtail catheter coming from the right brachial artery due to freshly operated right common femoral. B, Treatment of bilateral common iliac stenoses (right: proximal subtotal and left: more distal) with kissing balloon-kissing stent technique using brachial and left common femoral access. C, Postprocedural CO_2 angiography showing excellent primary success.

dioxide (CO_2) gas can be used as an alternative contrast agent, as it is absorbed almost instantaneously as opposed to other gases.[6] The image quality obtained with CO_2 may be limited in particular in small vessels such as below the knee (BTK) or in the pelvic arteries due to bowel gas motion (Figure 1). Despite easy accessibility of manual gas injection, this technique may not permit optimal control of the gas output in all cases.[7] However, interventions can be performed by integrating CO_2 and ICM. In order to optimize image quality when critically necessary, ICM is applied, while CO_2 is used for situations where image accuracy is not critical, aiming at decreasing the total amount of nephrotoxic ICM (CO_2-aided approach). Although CO_2 has been acknowledged for a long time as a safe alternative arterial contrast agent to guide peripheral procedures,[8,9] only a few studies have evaluated its efficacy in daily practice.[10-12]

Therefore, we investigated whether CO_2-aided percutaneous transluminal angioplasty (PTA) is an efficacious and safe method to decrease contrast volume during fluoroscopy-guided peripheral vascular procedures in routine angiological practice.

Materials and Methods

We retrospectively analyzed 191 consecutive patients (November 2012-December 2013) within the *Duesseldorf PTA Registry*, who were admitted for endovascular treatment of lower extremity PAD. The ethics board of Heinrich Heine University Duesseldorf approved the study protocol.

Procedures

Indications for peripheral endovascular treatment of PAD were based on current guidelines.[13] All patients had Doppler ankle–brachial index (ABI) measurements at rest and when possible after treadmill exercise. In patients with suspected or confirmed media sclerosis, segmental oscillography was performed. Furthermore, all patients received a thorough Duplex ultrasound examination to localize the flow-limiting stenosis and for sizing of later potential stent placement. Angiographic images were obtained via digital subtraction angiography (DSA) on a Philips Alura system with a flat panel detector. All patients with estimated glomerular filtration rate (eGFR) <60 mL/min received saline infusions starting the night before interventions at 1 mL/kg body weight/h for 12-hour preprocedure and 12-hour postprocedure. Metformin treatment was withheld for 48 hours prior to the procedure. All patients with successful peripheral procedures received dual platelet inhibition with acetylsalicylate and clopidogrel for 1 month following the procedure.

Conventional ICM Interventions

Conventional ICM (Visipaque 250, Amersham Buchler GmbH & CoKG, Braunschweig) was injected manually or via an assist pump using standard protocols. Briefly, DSA of the distal aorta and pelvic arteries was performed with a 15 mL bolus injected at 10 mL/s via a pigtail catheter located in the distal abdominal aorta. Images of the femoropopliteal or infrapopliteal (below the knee, BTK) segments were performed with 2 to 10 mL at 3 to 5 mL/s. The standard vascular X-ray protocol options preset by the manufacturer (Alura, Philips, Allura FD20, Philips, Hamburg, Germany) were used for pelvic (24 mAs, 80 kV, 3 frames/s), femoropopliteal (9 mAs, 70 kV, 3 frames/s), and BTK imaging (13 mAs, 65 kV, 1 frames/s).

Carbon dioxide-Aided PTA

Selection criteria for CO_2-aided peripheral interventions included an eGFR of <30 mL/min, with preserved urine excretion, contrast allergy, hyperthyroidism, or patient preference. Exclusion criteria for CO_2-aided peripheral interventions included chronic obstructive pulmonary disease stage Gold IV. In patients with absolute contraindications for ICM, CO_2 was

used as the exclusive contrast agent. These contraindications included hyperthyroidism. Carbon dioxide was injected via the same catheters as used for contrast. Briefly, the gas (Linde, Germany) was passed through a pressure-lowering valve (1.3 atm; Optimed, Ettlingen, Germany) via a 3-way valve into a special 100-mL syringe (Angioset; Optimed, Ettlingen, Germany) in which the piston could be fixed to accommodate a certain volume and hold the supra-atmospheric pressure. Via turning the 3-way valve in a second position, the syringe containing pressurized CO_2 gas was connected to the intra-arterial catheter. This allowed the gas to expand and passively flow through the intra-arterial catheter in the arterial lumen. Images were taken using DSA. In order to minimize bowel motion, patients expected to receive CO_2 angiography of the pelvic arteries received 20 mg butylscopolamine (Boehringer Ingelheim, Ingelheim, Germany) intravenously upon entering the catheterization laboratory. In order to allow better runoff and prevent proximal embolization of CO_2, the legs were elevated by 10° using a pillow placed under the lower part of the legs.The standard "vascular CO_2 Spezial" X-ray protocol options preset by the manufacturer (Alura, Philips) were used for pelvic (30 mAs, 80 kV, 3 frames/s), femoropopliteal, and BTK imaging (35 mAs, 65 kV, 3 frames/s).

Ankle–Brachial Index

The systolic and diastolic blood pressures were obtained automatically (Dynamap Vital Signs Monitor, Dinamap, General Electric Health Care, Solingen, Germany) on both arms. The systolic blood pressure in the distal anterior and posterior tibial arteries of both legs was measured using a nondirectional Doppler flow detector (Schabert Instrumente, Röttenbach, Germany) with a pencil probe (8 MHz). Arm and leg yielding the higher systolic pressure were used to calculate ankle–brachial index.

Assessment of Walking Distance by Treadmill

The walking distance was assessed in all patients before and after PTA. The walking distance was tested by a standardized protocol (slope: 12%, velocity: 3.2 km/h).[13] Relative walking distance was defined as the distance completed until pain started. The investigation was stopped with the onset of ischemic leg pain and the distance covered until was recorded as absolute walking distance.

Evaluation of CIN

We evaluated kidney function by serum creatinine concentrations and eGFR (Modification of Diet in Renal Disease) before and at days 1 and 2 after the intervention. CIN was defined by a rise in serum creatinine of >25% or >0.5 mg/dL.

Statistical Analyses

Results are expressed as mean ± standard deviation (SD). Comparisons between groups were analyzed by analysis of variance (gateway test) and, if significant, consecutive post hoc test (Bonferroni) was performed. Comparisons between 2 groups were performed with independent t test or χ^2 test for frequencies. Linear relationships between continuous variables were expressed as Pearson's r. Statistical significance was assumed at 2-tailed $P \leq .05$. All statistical analyses were performed using PASW Statistics 18.

Results

Study Population

A total of 191consecutive patients were treated for lower extremity PAD of the aortoiliac, femoral, popliteal as well as BTK disease. Of these, 154 received ICM only and 33 received $CO_2$with supplemental ICM. A total of 4 patients received only CO_2 due to overt hyperthyroidism or severe contrast agent allergy. The groups were comparable with regard to all epidemiological characteristics (Table 1) except for kidney function (ICM: 1.1 ± 0.6 mg/dL and 76 ± 28 mL/min, CO_2: 2.1 ± 1.3 mg/dL and 22 ± 34 mL/min, $P < .0001$ each) at admission. All interventions were performed by only 2 interventionalists (CH and ES) either alone or together.

Similar Procedural Success and Irradiation Time Between ICM and CO_2 in Claudicants and Patients With CLI

In general, CO_2 angiography was well tolerated. As we used manual passive injection, and it is very difficult to measure the amount of gas delivered to the patient. Several patients described temporary acute ischemic lower leg pain following both ICM and CO_2 injection once the respective contrast agent had passed the flow-limiting lesion and reached the ischemic lower leg. The pain subsided spontaneously within 20 seconds. One patient experienced acute dyspnea, and 1 patient experienced nausea following CO_2 injection. The latter 2 patients received an oxygen mask and were instructed to remain calm and hyperventilated. All symptoms subsided within 5 minutes.

Primary technical success was achieved in 100% of the CO_2-aided interventions and 148 (96%) of patients with ICM (Table 2; Figure 2). Irradiation (23 ± 16 minutes) and intervention (90 ± 37 minutes) times as well as the dose–area product were not significantly different between ICM and CO_2. A subgroup analysis showed that there was also no difference when evaluating claudicants (irradiation time: ICM 21 ± 16 minutes, CO_2: 24 ± 16 minutes; intervention time: ICM 73 ± 28 minutes, CO_2: 80 ± 33 minutes) and patients with CLI having Fontaine III or IV (irradiation time: ICM 25 ± 16 minutes, CO_2: 22 ± 12 minutes; intervention time: ICM 89 ± 34 minutes, CO_2: 83 ± 33 minutes).

Decreased Contrast Volume and Preserved Kidney Function With CO_2-Aided PTA

The amount of ICM used during interventions was significantly lower with CO_2-aided interventions (34 ± 41 mL) compared to ICM (113 ± 76 mL, $P < .001$; Figure 3). A subgroup analysis

Table 1. Patient Characteristics (*P* Values Refer to *t* Test).

	ICM	CO_2	*P*
n	154	37	
Age, years	70 ± 10	73 ± 12	.172
Male sex, n (%)	118 (77)	23 (62)	
Body mass index, kg/m^2	27 ± 6	27 ± 8	.471
Arterial hypertension, n (%)	136 (88)	30 (81)	
Hypercholesterolemia, n (%)	118 (77)	22 (59)	
Diabetes mellitus, n (%)	78 (51)	19 (51)	
Coronary artery disease, n (%)	110 (71)	24 (65)	
Smoker, n (%)	82 (53)	25 (68)	
Creatinine, mg/dL	1.1 ± 0.6	2.1 ± 1.3	<.001
Estimated glomerular filtration rate, mL/min	76 ± 28	22 ± 34	<.001
Chronic kidney failure, n (%)	55 (36)	31 (84)	
Chronic kidney disease stage, n (1/2/3/4/5)	(45/65/38/4/2)	(2/3/16/13/3)	
Total cholesterol, mg/dL	182 ± 95	158 ± 79	.079
Fasting plasma glucose, mg/dL	122 ± 53	115 ± 33	.486
Hemoglobin$_{A1c}$ (%)	7.1 ± 3.0	7.0 ± 2.3	.792
Acetylsalicylic acid, n (%)	138 (90)	37 (100)	
Clopidogrel, n (%)	135 (88)	32 (86)	
Coumadin, n (%)	23 (15)	10 (27)	
Angiotensin-converting enzyme inhibitor, n (%)	63 (41)	17 (46)	
Angiotensin receptor blocker, n (%)	42 (27)	7 (19)	
Beta-blocker, n (%)	103 (67)	31 (84)	
Statin, n (%)	118 (77)	26 (70)	
Fontaine IIb, n (%)	95 (62)	16 (43)	
Fontaine III, n (%)	13 (8)	3 (8)	
Fontaine IV, n (%)	46 (30)	18 (49)	
Walking distance relative, m	65 ± 42	56 ± 35	.566
Walking distance absolute, m	99 ± 66	82 ± 56	.497
Ankle brachial index rest	0.59 ± 0.24	0.66 ± 0.28	.382
Ankle brachial index after exercise	0.32 ± 0.14	0.32 ± 0.26	.398
		MV ± SD	

Abbreviations: ICM, iodinated contrast medium; CO_2, carbon dioxide; SD, standard deviation.

Table 2. Procedure Related Characteristics and Outcomes.

	ICM	CO_2	*P*
Iliac arteries, n (%)	57 (37)	8 (22)	
Femoral arteries, n (%)	69 (45)	13 (35)	
Popliteal arteries, n (%)	7 (5)	6 (16)	
Below-the-knee, n (%)	21 (14)	10 (27)	
Plain balloon angioplasty, n (%)	41 (27)	13 (35)	
Stents, n (%)	111 (72)	24 (65)	
Recanalization, n (%)	51 (34)	16 (43)	
Primary technical success, n (%)	148 (96)	37 (100)	
Irradiation time, min	23 ± 17	22 ± 14	.606[a]
Area dose product, cGy × cm^2	9359 ± 11 474	8054 ± 12 764	.865[a]
Intervention time, min	79 ± 37	83 ± 32	.747[a]
Contrast medium, mL	112 ± 76	34 ± 41	<.001[a]
Creatinine postprocedural day 1, mg/dL	1.1 ± 0.6	2.0 ± 0.9	<.001[a]
Creatinine postprocedural day 2, mg/dL	1.3 ± 0.6	2.3 ± 0.9	<.001[a]
eGFR postprocedural day 1, mL/min	73 ± 28	37 ± 22	<.001[a]
eGFR postprocedural day 2, mL/min	62 ± 25	30 ± 12	<.001[a]
Contrast induced nephropathy, n (%)	29 (19)	2 (5)	.044[b]
Walking distance relative, postprocedural, m	77 ± 50	76 ± 53	.214[a]
Walking distance absolute, postprocedural, m	119 ± 80	84 ± 38	.016[a]
ABI rest, postprocedural	0.70 ± 0.25	0.89 ± 0.26	.011[a]
ABI after exercise, postprocedural	0.45 ± 0.27	0.59 ± 0.25	.055[a]
		MV ± SD	

Abbreviations: ICM, iodinated contrast medium; CO_2, carbon dioxide; eGFR, estimated glomerular filtration rate; ABI, ankle brachial index; SD, standard deviation.
P value refers to:
[a]*t*-test or
[b]χ^2 test.

showed that this was true in both claudicants (CO_2: 49 ± 53 mL, ICM: 125 ± 79 mL) and patients with CLI (CO_2: 24 ± 23 mL, ICM: 95 ± 65 mL). A different subgroup analysis showed that the contrast volume was significantly lower in CO_2 than in ICM when comparing intervention within individual vessel segments (Table 3). The contrast volume used in the popliteal ICM procedures were significantly lower as compared with interventions of the aortoiliac segment (Table 3). Please note that in both ICM and CO_2 groups 15% and 12% of procedures, respectively, involved additional treatment of the downstream segment to facilitate runoff (data not shown). As shown in Table 1, patients in the CO_2 group exhibited significant lower kidney function at baseline.

In the ICM group, CIN occurred in 29 (19%) patients and in 2 patients in the CO_2 group (5%, $P = .044$). A subgroup analysis showed that within the CO_2 group claudicants did not experience a single CIN, whereas 2 patients with CLI developed CIN. All cases were successfully treated with saline infusion without the need for initiation of hemodialysis and recovered spontaneously within 4 days.

As approximately half of the patients in each group were diabetic, we performed an additional subgroup analysis. This showed that in the ICM group diabetic patients experienced a significantly higher rate of CIN (25%) compared to patients without diabetes (13%) at a similar baseline creatinine of 1.1 ± 0.7 mg/dL and 1.1 ± 0.5 mg/dL, respectively, and similar amounts of contrast medium. Within the CO_2 group, CIN in diabetic patients (5%) and patients without diabetes (6%) did not differ.

Discussion

This study presents real-life data from all patients receiving endovascular treatment for PAD in our institution over

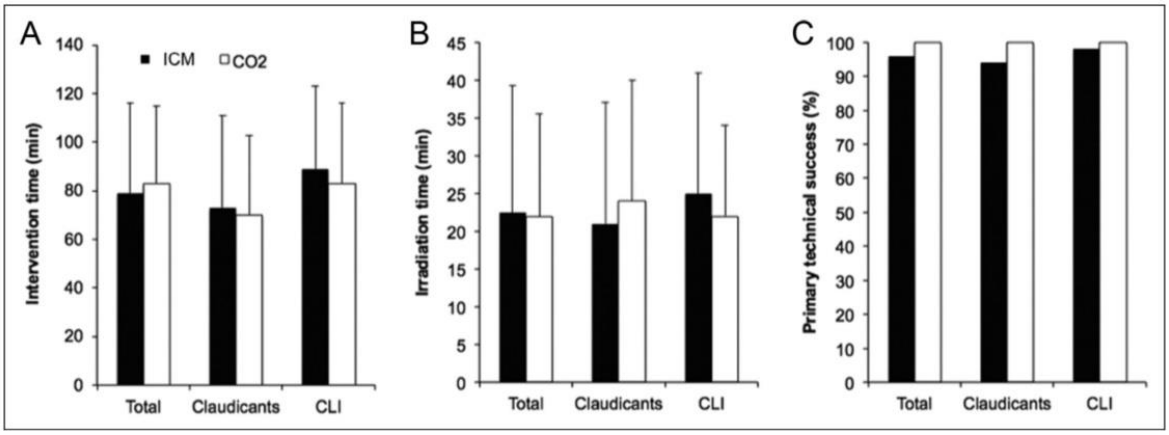

Figure 2. (A) Intervention time, (B) irradiation time, and (C) technical success. Results are comparable between conventional contrast medium (iodinated contrast media [ICM]) and CO_2-aided intervention in overall patients and on subgroup analysis both in claudicants (Fontaine IIb) and in patients with CLI (Fontaine III-IV). No significant differences were found between the groups.

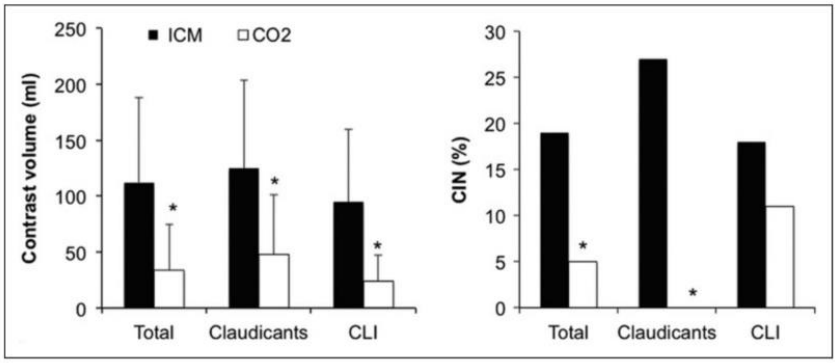

Figure 3. (A) Contrast volume and (B) frequency of contrast-induced nephropathy (CIN) in iodinated contrast media [ICM] and CO_2 group. The necessary contrast volume and incidence of CIN was significantly lower with CO2-aided percutaneous transluminal angioplasty (PTA) in total and in subgroups of both claudicants and patients with critical limb ischemia (CLI). * $P < .05$ vs ICM (A: *t* test for total and 1-way analysis of variance [ANOVA] for subgroup analysis, B: χ^2 test for individual group comparisons).

Table 3. Amount of Iodinated Contrast Medium (mL) Arranged by Treated Vessel Segment.[a]

	All	ICM[b]	CO_2[c]	*P*
Iliac, n	109 ± 58 (65)	118 ± 54[d] (57)	48 ± 49 (8)	.001
Femoral, n	92 ± 58 (82)	104 ± 53 (69)	26 ± 26 (13)	<.001
Popliteal, n	50 ± 33 (13)	72 ± 20 (7)	25 ± 28 (6)	.01
BTK, n	73 ± 71 (31)	93 ± 77 (21)	31 ± 21 (10)	.001
			MV ± SD	

Abbreviations: ANOVA, analysis of variance; ICM, iodinated contrast medium; CO_2, carbon dioxide; SD, standard deviation; LSD, least significant difference; BTK, below the knee.
[a]Overall 1-Way ANOVA $P < .001$; *P* value ICM vs CO_2.
[b]15% and [c]12% of procedures involved additional treatment of downstream segment.
[d]$P = .048$ vs popliteal ICM, LSD post hoc test.

1 year illustrating that CO_2-aided angiography is an effective method to guide peripheral procedures helping to prevent CIN.

Only few studies have evaluated the efficacy of CO_2-aided angiography in daily practice.[10-12] One recent Japanese registry study has assessed the safety and efficacy of CO_2 angiography-guided endovascular therapy for renal and stable iliofemoral artery disease.[10] They showed in 98 patients with a baseline eGFR of 35 mL/min that CO_2 angiography-guided angioplasty was effective (97.5% primary technical success rate) for preventing CIN. With an average additional dose of ICM of 15 mL, they observed 5% CIN but also 17% CO_2 angiography-related complication. In our current study, we confirm these data with a similar technical success rate (100%), slightly higher overall dose of contrast (35 mL), and similar rates of

CIN (5%) in the CO_2-aided group. However, we only observed minor temporary CO_2 angiography-related side effects (ischemic pain, dyspnea, and nausea), which resolved within minutes. Of note, acute ischemic lower leg pain is a common side effect of both ICM and CO_2 when injected proximal to a severe stenosis. While it can be related to injection pressure, we submit that it was in most of our patients rather due to the temporary displacement of oxygen-saturated blood from the arteries as it did not occur immediately during injection of CO_2 but shortly thereafter when the CO_2 reached the ischemic part of the lower leg. Interestingly, we frequently observe in both ICM and CO_2 that these acute pain symptoms do no longer occur after injection when the revascularization procedure was successful. Taken together, we extend the Japanese data [10] and a more recent study[12] by showing that CO_2 angiography can also be safely and efficaciously used in the treatment of popliteal and BTK interventions and also in patients with CLI (Fontaine III and IV) if individual image quality allows. However, the magnitude of benefit may differ between groups of patients. When evaluating patients with claudication, not a single CIN occurred with CO_2, whereas significantly more CIN was observed after treatment of patients with CLI. As an additional novelty of our present study, we present the CO_2 results as part of an allcomers group side by side with patients receiving only conventional ICM as a control group.

Limitations of using CO_2 as a contrast agent consist of a somewhat lower quality of angiograms compared to DSAs applying conventional ICN and of frequently perceived longer procedure durations.[14] This may be related to the manual injections and to the postprocessing imaging analysis. More adequate opacification of the arteries may be obtained with optimized injection technique including optimized CO_2 pressure and volume injections and X-ray protocols. However, our current data show that these disadvantages can be avoided using a combined approach. Due to potential inaccuracy of CO_2 with regard to diameter quantification,[15,16] sizing of stents was mostly performed by preprocedural ultrasound and by balloon sizing. In many cases, in the absence of absolute contraindications for ICM, we performed focused diagnostic evaluations with conventional contrast agent at the beginning and end of the procedures. Additional runs for wire guidance, setting of road maps, and stent placement were performed with CO_2. Our data demonstrate that the ICM and CO_2-aided approaches can be performed with similar intervention and irradiation times at an almost perfect primary technical success rate. This, however, could only be accomplished by an extensive preinterventional ultrasound examination performed by experienced sonographers. In summary, our CO_2-aided approach combines the advantages of both contrast agents in routine practice achieving optimal interventional results, with short procedural time, while avoiding further injury to predamaged kidneys in the most vulnerable patients by effectively lowering the amount of harmful ICM using CO_2 as supplemental contrast. Nevertheless, it may be argued that CO_2-alone angiography should be used as the initial contrast agent for the evaluation of PAD in patients with renal failure, and CO_2-aided ICM angiography should be considered only if the quality of the images is poor.

Important study limitations apply to the study design including retrospective analysis and lack of blinding and significant differences between the study populations of the ICM and CO_2 groups. Inherently, major limitations of retrospective study design include that there is frequently an absence of data on potential confounding factors, and it may be difficult to identify an appropriate exposed cohort and an appropriate comparison group. However, the fact that the baseline kidney function was significantly lower in the CO_2 group rather strengthens our main message that the CO_2-aided approach can preserve kidney function in the context of peripheral vascular interventions.

Conclusions

The present analysis underscores the value of CO_2 as an alternative contrast agent that can be used routinely to lower contrast volume and prevent CIN during peripheral vascular procedures from the iliac down to BTK even in patients with CLI.

Author Contribution

All authors contributed to (1) conception and design, or acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Vascular dysfunction of brachial artery after transradial access for coronary catheterization: impact of smoking and catheter changes

Heiss C, Balzer J, Hauffe T, Hamada S, **Stegemann E**, Koeppel T, Merx MW, Rassaf T, Kelm M, Lauer T

JACC Cardiovasc Interv. 2009;2(11):1067-1073

Transradiale Herzkatheteruntersuchungen als Alternative zum transfemoralen Zugangsweg nehmen aufgrund geringer lokaler Komplikationsraten zu. Postinterventionelle Funktionsveränderungen der Radialarterie sind beschrieben und werden durch das geringe Gefäßkaliber und die mechanische Irritation erklärt. In dieser Arbeit wird gezeigt, dass auch die kaliberstärkere Brachialarterie über eine längere Zeit nach transradialer Untersuchung eine eingeschränkte Funktion aufweist, und zwar umso stärker je mehr Katheterwechsel während der Untersuchung durchgeführt wurden.

JACC: CARDIOVASCULAR INTERVENTIONS
© 2009 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.
VOL. 2, NO. 11, 2009
ISSN 1936-8798/09/$36.00
DOI: 10.1016/j.jcin.2009.09.010

Vascular Dysfunction of Brachial Artery After Transradial Access for Coronary Catheterization

Impact of Smoking and Catheter Changes

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Objectives The aim of this study was to investigate the effect of diagnostic transradial catheterization on vascular function of upstream brachial artery (BA).

Background The transradial access has recently become an alternative to transfemoral cardiac catheterization. A potential caveat of this approach lies in possible sustained physical radial artery (RA) damage.

Methods We studied 30 patients (age 61 ± 11 years) undergoing diagnostic coronary angiography with the transradial access (5-F). Endothelium-dependent, flow-mediated vasodilation (FMD) was measured before and at 6 and 24 h after catheterization of the right-sided RA and BA with high-resolution ultrasound. The left-sided RA served as a control.

Results Transradial catheterization significantly decreased FMD in the RA (overall mean 8.5 ± 1.7% to 4.3 ± 1.6%) and the upstream BA (overall mean 4.4 ± 1.6% to 2.9 ± 1.6%) at 6 h. Subgroup analysis showed that FMD of both arteries at 6 h was significantly lower in active smokers and that it only remained impaired at 24 h in this group, whereas nonsmoker FMD fully recovered. The degree of BA but not RA FMD dysfunction was related to the number of catheters used, with no change after 2 catheters, 1.9 ± 1.2% decrease (6 h) and recovery (24 h) after 3 catheters, and 3.9 ± 1.2% decrease (6 h) without recovery (24 h) after 4 to 5 catheters. The RA dysfunction correlated with the baseline diameter. The contralateral control RA exhibited no change ruling out systemic effects.

Conclusions Transradial catheterization not only leads to dysfunction of the RA but also the upstream BA, which is more severe and sustained in smokers and with increasing numbers of catheters. (J Am Coll Cardiol Intv 2009;2:1067–73) © 2009 by the American College of Cardiology Foundation

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This work was supported by grants from the Deutsche Forschungsgemeinschaft (RA 969/4-1 to Dr. Rassaf; KE 405/5-1 to Dr. Kelm; and GRK 1089, TP 3 to Drs. Rassaf and Kelm), Klinische Forscherkomission to Dr. Lauer, Hans und Gertie Fischer Stiftung to Dr. Lauer, and American Heart Association to Dr. Heiss. Drs. Heiss and Balzer contributed equally.

Manuscript received August 28, 2009, accepted September 23, 2009.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 11, 2009
NOVEMBER 2009:1067–73

Flow-mediated vasodilation (FMD) of the brachial artery (BA) represents the most widely accepted noninvasive standard method for the assessment of endothelial dysfunction, which is suggested to play a significant role in the development and progression of atherosclerosis (1–3). The FMD measurement has gained growing interest as several studies indicated that a decreased FMD response predicts arterial disease progression with intimal thickening and increased cardiovascular mortality (4,5). Several cardiovascular risk factors have been shown to lead to acute and chronic FMD impairment (2,6). Physical damage to the vascular endothelium might also be a cause of functional impairment and might lead to arterial disease (7). In the context of BA FMD, this is particularly important, because the transradial route to perform coronary angiograms and percutaneous coronary interventions is an emerging safe alternative to the femoral access due to its lower bleeding complications (8–10). In animal and human studies, oversized sheaths have been demonstrated to chronically impair endothelial and smooth muscle cell function, leading to intimal thickening and luminal loss potentially impacting the quality of the radial artery (RA) as a bypass graft for coronary artery bypass grafting surgery in patients with coronary artery disease (CAD) (11–13). However, whether catheterization might also affect other vessels also being in contact with the catheter, including the BA, and which factors determine the functional recovery are unclear.

Abbreviations and Acronyms

ANOVA = analysis of variance
BA = brachial artery
CAD = coronary artery disease
FMD = flow-mediated vasodilation
GTN = glycerol trinitrate
RA = radial artery
WSS = wall shear stress

In this study, we hypothesize that routine cardiac diagnostic catheterization causes a vascular dysfunction not only to the radial but also to the BA. In a proof-of-concept study, we noninvasively studied the effect of transradial diagnostic cardiac catheterization on endothelium-dependent and endothelium-independent vasodilation of the BA and RA in patients.

Methods

Study design. We measured endothelium-dependent FMD and nitroglycerin-mediated endothelium-independent vasodilator function in the RA and BA before as well as 6 and 24 h after right-sided transradial cardiac catheterization (sheath removal) in patients undergoing diagnostic coronary angiography. The contralateral left RA served as a control.

Study population. We included 30 consecutive patients undergoing diagnostic coronary angiography with suspected CAD. Patients were excluded from the study if they had undergone previous radial cannulation or had an abnormal Allen test result consistent with insufficient ulnar collateral supply. Other exclusion criteria were acute inflammation (C-reactive protein >0.5 mg/dl), malignancies, heart rhythm other than sinus rhythm, and heart failure New York Heart Association functional class III to IV. All patients provided informed consent, and the study protocol was approved by the local ethics board.

Transradial cardiac catheterization. The right RA was cannulated with a 5-F (external diameter 2.29 mm), 7-cm-long sheath (Cordis, Johnson & Johnson, Piscataway, New Jersey). After sheath insertion, all patients received 0.2 mg nitroglycerin intra-arterially to prevent vasospasm and 5,000-IU heparin intravenously to prevent thrombosis. The angiography was performed with a monoplane X-ray system. Primarily, a Judkins left 3.5 catheter was used for the left coronary artery, and a Multipurpose catheter was used for the right coronary artery and the left ventricular angiogram. If necessary, further catheters included Judkins left 4 and 5, Amplatz left 1, and Judkins right 4 and 5. At the end of the procedure, the sheath was removed immediately, and a wrist clamp (Terumo, Eschborn, Germany) was applied for 4 h (13 ml).

Determination of vascular function with ultrasound. Images were acquired with high-resolution ultrasound (Vivid I, GE Healthcare, Milwaukie, Wisconsin) with a 15-MHz linear probe consistent with the current guidelines (3) and as previously described (6,14,15). Briefly, baseline studies were performed from 7:00 AM to 8:00 AM in an air-conditioned room with constant temperature. At each time point, the left (noncannulated) and right (cannulated) RA functions as well as right BA vasodilator functions were assessed with FMD and glycerol trinitrate (GTN).

MEASUREMENT OF FMD. RA function was determined at a landmark 2 to 3 cm proximal the sheath insertion point. Baseline heart rate and blood pressure were recorded. Baseline measurements included RA diameter and RA flow velocity. Subsequently, a blood pressure cuff was inflated at the forearm to suprasystolic pressures for 5 min. Upon cuff release, the RA flow measurements were repeated to demonstrate hyperemia. The RA diameter was measured 60 to 90 s after cuff deflation. The opposite arm and the right BA were measured in the same fashion. The sequence was in random order.

DETERMINATION OF GTN. Sublingual nitroglycerin (0.4 mg) was administered. Repeat flow and diameter measurements were recorded for both arms at 4 min to assess endothelium-independent vasodilation.

IMAGE ANALYSIS, CALCULATION OF VASODILATION, AND WALL SHEAR STRESS (WSS). The image and flow analyses were performed offline from recorded loops with an automated system (Brachial Analyzer 5, Medical Imaging Applications, Coralville, Iowa). All diameter readings were taken at diastole, and flow velocity represents the mean angle-corrected Doppler flow velocity. Vasodilation results are presented as percent change: (Diameter$_{\text{postischemia}}$ –

Diameter $_{baseline}$/Diameter$_{baseline}$) × 100. Flow was calculated as $\pi \times$ (Diameter/2)2 × flow velocity (V). Hyperemic blood flow after occlusion of the forearm increases WSS in the RA and BA, which leads to FMD. The WSS was calculated at peak flow (onset of reactive hyperemia) as: $8 \times \mu \times$ V/Diameter, where blood viscosity (μ) was assumed to be constant at 0.035 dyne × s/cm^2. Images were assessed by 1 experienced investigator blinded to the study regime.

Statistical analyses. Results are expressed as mean ± SD. The primary test for overall time-dependent effects was a 1-way repeated measurement analysis of variance (ANOVA). To test for the effects of smoking status and number of catheters, a 2-way repeated measurements ANOVA was performed, with time being the intra-subject factor and smoking status or number of catheters being between-subject factors. The ANOVA and unadjusted Holm-Sidak post hoc tests were computed with SigmaStat 3.5 (Systat Software, Inc., San Jose, California).

Results

The characteristics of the study population are summarized in Table 1. There was no difference in mean arterial pressure and heart rate between the study time points (Table 2), excluding sympathetic activation of study subjects. The mean catheterization time was 16 ± 16 min, and the necessary mean volume of contrast agent was 97 ± 49 ml. The number of catheters used varied between 2 and 5 (16 × 2, 10 × 3, 3 × 4, 1 × 5 catheters). No vascular complications including bleeding or vasospasm occurred in the patients.

Endothelial dysfunction in BA and RA after transradial cardiac catheterization. The experimental set-up and overall results are depicted in Figure 1 (solid bars: right RA, hatched bars: right BA, open bars: left RA; 1-way ANOVA). Baseline FMD was 4.4 ± 1.6% in the right BA, 8.5 ± 1.7% in the right RA, and 8.9 ± 2.2% in the left RA ($p = 0.56$ between RAs) and comparable to previous studies performed in CAD patients with already impaired vasodilator function at baseline (6). Whereas FMD did not change in the control (left RA), FMD was significantly decreased in the right intervention arm at 6 h (BA: 2.9 ± 1.5%; RA: 4.3 ± 1.6%). At 24 h, RA FMD recovered significantly but was still impaired as compared with baseline values (RA: 6.8 ± 2.0%, $p < 0.001$ vs. 6 h and baseline). Overall, BA FMD remained impaired at 24 h (3.3 ± 1.6%, $p = 0.003$ vs. baseline, $p = 0.247$ vs. 6 h).

The baseline diameter of the BA and RA was unchanged at 6 h (Table 2). At 24 h, the baseline diameter of the BA (4.41 ± 0.81 mm) and RA (2.75 ± 0.48 mm) but not the left-sided control RA was significantly increased (BA: 4.61 ± 0.81 mm, $p = 0.026$ vs. baseline; RA: 2.88 ± 0.42 mm, $p = 0.004$ vs. baseline). Because WSS during reactive hyperemia is an important determinant of FMD, depending on the diameter and flow velocity (16,17), we calculated the local instantaneous WSS. The local WSS induced at the onset of reactive hyperemia was not altered by the intervention (baseline: 73 ± 20 dyne/cm^2 [right RA], 82 ± 21 dyne/cm^2 [left RA], 64 ± 23 dyne/cm^2 [right BA]). This suggests that the stimulus for FMD in the BA and RA that depends on the ischemic vasodilator response of the downstream microvasculature is unaltered by the intervention (16,17). This supports the notion that the catheterization indeed causes conduit artery dysfunction, and the results cannot be explained by downstream phenomena, including embolization and/or inflammatory alterations of the microcirculation.

To determine the contribution of endothelium-dependent vasomotor dysfunction to the impairment of FMD after catheterization, we measured the endothelium-independent smooth muscle response to oral GTN after FMD. Our results show that the GTN response significantly decreased in both BA and RA at 6 h (RA: 12.7 ± 2.4% [baseline] vs. 7.5 ± 2.0% [6 h], $p < 0.001$; BA: 13.1 ± 4.2% [baseline] vs. 8.7 ± 3.5% [6 h], $p = 0.001$ vs. baseline). The

Table 1. Characteristics of Study Population

n (M/F)	30 (19/11)
Age (yrs)	61 ± 11
BMI (kg/m^2)	31 ± 7
Pack-yrs	22 ± 19
Glucose (mg/dl)	101 ± 23
HbA1c (mg/dl)	5.6 ± 0.2
Triglycerides (mg/dl)	217 ± 150
Total cholesterol (mg/dl)	184 ± 49
HDL cholesterol (mg/dl)	61 ± 30
LDL cholesterol (mg/dl)	126 ± 27
Creatinine (mg/dl)	0.7 ± 0.0
Hematocrit (%)	43 ± 1
Statins (%)	60
ACE inhibitors (%)	63
Calcium-channel blockers (%)	7
Oral nitrates (%)	27
Diuretics (%)	27
Beta-blockers (%)	83
Acetylsalicyclic acid (%)	87
Clopidogrel (%)	27
Positive family history of CAD (%)	33
CAD (%)	80
History of myocardial infarction (%)	43
History of PCI (%)	50
Arterial hypertension (%)	23
Obesity (%)	23
Hypercholesterolemia (%)	73
Diabetes mellitus (%)	10
Smoking (%)	40
Former smokers (%)	33

ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention.

Table 2. Hemodynamic Parameters

	B	6 h	24 h	p Value
Heart rate (beats/min)	76 ± 27	74 ± 22	72 ± 22	0.566
MAP (mm Hg)	110 ± 19	109 ± 16	107 ± 16	0.354
Diameter (mm)				
Right RA	2.75 ± 0.46	2.80 ± 0.54	2.88 ± 0.55*	0.003
Right BA	4.41 ± 0.81	4.49 ± 0.83	4.61 ± 0.81*	0.008
Left RA	2.82 ± 0.37	2.81 ± 0.39	2.84 ± 0.42	0.389

*p < 0.05 versus baseline reading before catheterization (B).
BA = brachial artery; MAP = mean arterial pressure; RA = radial artery.

decrease in GTN mediated endothelium-independent vasodilation (BA: −3.5 ± 5.2%, RA: −5.3 ± 3.0%) was not dependent on the number of catheters used. At 24 h, the GTN response recovered partially in the RA (10.0 ± 2.3%, p < 0.001 vs. baseline and 6 h) but remained impaired in the BA (9.5 ± 3.7%, p = 0.005 vs. baseline, p = 0.441 vs. 6 h).

We calculated the ratio of FMD and GTN response to determine the relative contribution of endothelium-dependent to total GTN-mediated vasodilation. This showed a significant decrease from 0.73 ± 0.14 (baseline) to 0.58 ± 0.16 (6 h) and recovery to 0.73 ± 0.16 (24 h) in the right RA, suggesting temporary endothelium-dependent vasodilator dysfunction and that the still-decreased FMD response at 24 h is primarily due to reduced smooth muscle responsiveness. In contrast, FMD/GTN ratio in the BA only tended to decrease at 6 h but did not reach statistical significance during the whole study period. Both GTN response and FMD/GTN ratio were unaffected by the intervention in the control arm. No correlations were observed between the degree of vascular functional impairment and the duration of interventions or volume of contrast media.

BA dysfunction is related to number of catheter changes, and RA dysfunction is related to baseline diameter. The BA FMD decreased progressively with increasing mechanical

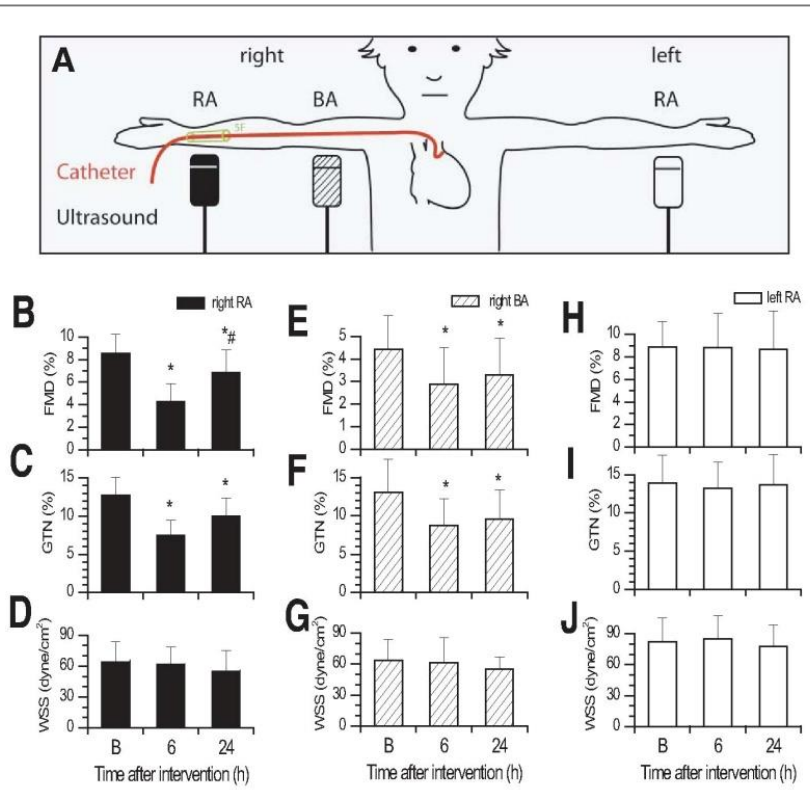

Figure 1. Functional Impairment of Conduit Arteries After Transradial Coronary Angiography

(A) Schematic of experimental setup: after cannulation of the right radial artery (RA), a coronary angiography catheter is advanced through the RA and brachial artery (BA), and coronary angiography is performed. **(B to G)** This leads to impairment of endothelium-dependent and glycerol trinitrate (GTN)-induced endothelium-independent vasodilator function. The lack of change in wall shear stress (WSS) representing the driving force for endothelium-dependent flow-mediated vasodilation (FMD) suggests that the injury did not affect the microvasculature and was therefore rather located in the macrovasculature response to WSS. **(H to J)** Function of the left contralateral RA is used as a control and remained unchanged. *p < 0.05 vs. baseline; #p < 0.05 vs. 6 h (1-way analysis of variance). B = baseline reading before catheterization.

manipulation, depending on the number of catheter changes (Fig. 2) (2-way ANOVA, p = 0.001). Although BA FMD did not significantly change at 6 h after 2 catheters (Delta FMD −0.1 ± 0.8%), it was progressively decreased after 3 (−1.9 ± 1.2%, p = 0.003 vs. baseline) and 4 to 5 catheters (−3.9 ± 1.0%, p = 0.005 vs. baseline). At 24 h, BA FMD after 3 catheters recovered to baseline values, whereas BA FMD after 4 to 5 catheters remained significantly impaired. In contrast, the RA FMD decreased independent of the number of catheters used (−4.3 ± 1.5%, p = 0.845), potentially due to relative protection by the arterial sheath from further injuries induced by catheter changes. As opposed to the degree of BA dysfunction, the degree of RA dysfunction at 6 h inversely correlated with the baseline diameter, suggesting that sheath insertion leads to a greater dysfunction in smaller-sized vessels (r = 0.49, p = 0.018).

Recovery of function is impaired in active smokers. Because our previous studies have suggested that cigarette smoke exposure might have an impact on vascular regenerative processes (18), we performed a subgroup analysis comparing the FMD responses in active smokers and nonsmokers (Figs. 2C and 2D). There was no significant difference in baseline FMD values between the groups. In active smokers, 6- and 24-h FMD values were significantly lowered in both BA and RA as compared with baseline and respective time-points in nonsmokers. In nonsmokers, 24-h BA and RA FMD was not significantly different from baseline values, suggesting completed functional recovery in this group.

Discussion

The key findings of the present report are that BA function is impaired along with RA function after transradial cardiac catheterization with a 5-F sheath. Moreover, the degree of BA impairment and recovery was determined by the num-

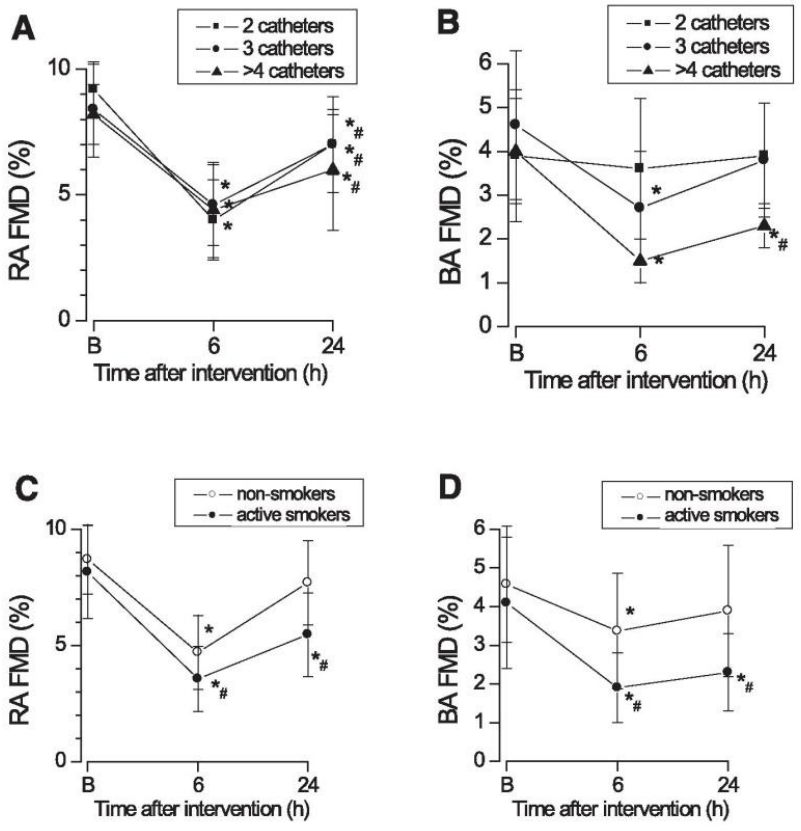

Figure 2. Vascular Dysfunction Depends on Number of Catheters and Smoking Status

The degree of vascular dysfunction expressed as a decrease in FMD at 6 h and recovery at 24 h as compared with baseline after transradial cardiac catheterization is correlated to the number of catheters used in the **(B)** BA but not the **(A)** RA likely due to relative protection from further injury by the sheath, which was at the site of RA FMD measurements. *p < 0.05 vs. 2 catheters; #p < 0.05 vs. 3 catheters. Furthermore, **(C and D)** smokers exhibit a significantly greater degree of dysfunction that does not recover within the observation period of 24 h. *p < 0.05 vs. baseline; #p < 0.05 vs. nonsmokers (2-way analysis of variance). Abbreviations as in Figure 1.

ber of catheters used and current smoking status, whereas the RA dysfunction was related to the RA baseline diameter.

Brachial vasodilator dysfunction after transradial catheterization. No study so far has tested the vasodilator function of the BA after being navigated with the catheter en route to the coronary arteries. We show here for the first time that BA function is impaired after transradial catheterization. Importantly, the degree of BA dysfunction depended on the magnitude of mechanical manipulation as indicated by the number of catheters used. Although BA FMD did not significantly decrease when 2 catheters were used, 3 catheters caused severe yet reversible impairment of BA function, and 4 to 5 catheters caused even more severe and sustained impairment of BA function throughout the observation period of 24 h. These results are in line with classical experimental results showing that small lesions can be covered by spreading and migration of surrounding endothelial cells, whereas larger areas require endothelial proliferation (11). Our present results might have clinical consequences for these patients. First, measuring FMD as a surrogate end point in the catheterized arm might yield false results. Second, mechanical injury has been shown to lead to adverse remodeling. In animal models of arteriosclerosis, denudation of arteries leads to plaque development. In patients, repeated transradial catheterization was shown to lead to intimal thickening and luminal loss of the RA (13). Catheter-related mechanical injury might promote arteriosclerosis even in vessels that otherwise are relatively spared from this disease. Clinical implications are that the number of catheter changes should be minimized to avoid unnecessary injury to the vessel walls.

Smoking leads to slower recovery. We and others have previously shown that cigarette smoke exposure leads to acute impairment of endothelial function and might also have a longer-lasting negative impact on vascular repair mechanisms, including the migratory function of endothelial cells and endothelial progenitor cells (18,19). In the context of the present study, we showed that in active smokers the impairment of endothelial function caused by mechanical irritation and likely physical injury to the endothelium is more severe and the recovery is slower as compared with nonsmokers. Impaired migration of endothelial cells and endothelial progenitor cells in the process of covering the denuded areas might contribute to slower repair. Furthermore, it is likely that a similarly impaired recovery occurs in other areas that are in contact with the catheter, including the coronary orifices. This underscores the necessity to enforce strict smoking cessation and even prevent secondhand smoke exposure in patients undergoing catheterization.

Sheath size determines recovery after radial injury. In the current published reports there are conflicting data regarding the vascular injury inflicted upon the RA by insertion of a sheath during cardiac catheterization. This is important, because this might affect the quality of the RA as a potential bypass graft for coronary artery bypass grafting surgery. It was shown that FMD of the RA is virtually abolished at least for 6 to 10 months after catheterization when 6-F sheaths are used (12,20). One study showed that insertion of a 4-F sheath does not cause a decrease in FMD at 24 h, suggesting that the greater the size of the sheath the greater the inflicted injury to the RA (20). In the present study, a 5-F sheath was used, which is in range of physiologic RA diameter. We observed an inverse correlation between the degree of functional RA impairment and baseline diameter, supporting the notion that vasodilator function of the RA can recover within 24 h (in nonsmokers) and that relatively small-sized sheaths should be used to ensure minimal injury and fast recovery of the RA.

Determinants of vascular dysfunction. Mechanistically, our results suggest that the vascular dysfunction caused by transradial catheterization is not an isolated injury to the endothelium but also to the smooth muscle compartment with impaired responsiveness toward the vasodilator nitroglycerin. Endothelial dysfunction as indicated by decreased FMD might be explained in part by the lower responsiveness of the smooth muscle compartment. This dysfunction is most likely caused by the mechanical irritation of the vascular wall during the sheath insertion and removal, because there was no change in vascular vasodilator function in the contralateral arm. An alternative explanation might be an impaired responsiveness due to high local concentrations of nitroglycerin, which is given as a single bolus injection immediately after sheath placement to prevent vasospasm and would not necessarily affect the left-sided arteries. This possibility and the possible influence of sympathetic activation are ruled out because heart rate and blood pressure did not change, 6-h baseline diameters of right-sided arteries were not significantly greater than at baseline, there was no significant impairment of BA FMD when only 2 catheters were use, and as discussed in the preceding text, left-sided measurements remained unaffected.

Conclusions

Collectively, our results suggest that transradial catheterization leads to dysfunction not only of the RA but also the upstream BA. Clinical implications are that the number of catheters used should be kept to a minimum, strict smoking cessation should be enforced, and sheath size should be matched to the radial arterial diameter to protect vascular function and prevent potential arterial degeneration in the future. Furthermore, FMD measurements as a surrogate of cardiovascular health need to be interpreted with caution after transradial catheterization.

Acknowledgment

The authors thank Dr. Yerem Yeghiazarians for helpful discussions.

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Key Words: flow-mediated dilation ■ transradial cardiac catheterization ■ vascular dysfunction.

V Methodik

Das Herzkatheterlabor hat als Herzstück der interventionellen Kardiologie hohe Priorität im Ablauf einer modernen kardiologischen Abteilung. Daher ist dessen reibungsloser Ablauf inklusive optimaler Vor- und Nachbereitung der Katheteruntersuchungen meist im Zentrum des Interesses der gesamten Abteilung. Mit einem Wechsel in der Klinikleitung, welcher im Dezember 2005 vollzogen wurde, erfolgte daher in der untersuchten Herzkatheter Einheit unter Führung der neuen Klinikleitung und entsprechend den Empfehlungen der Deutschen Gesellschaft für Kardiologie[35] sehr rasch die Erarbeitung von klaren Prozessabläufen beziehungsweise von Checklisten, welche ab Januar 2006 ihre Umsetzung fanden.

Die im Folgenden beschriebenen Prozesse laufen im Umfeld eines High-Volume-Herzkatheter Labors an einer Universitätsklinik ab. Die eingesetzten Standard Operating Procedure (SOP) beinhalten eine verbindliche textliche Beschreibung der Abläufe. Hierfür werden für Teilbereiche (Herzkatheter Vorbereitung, Komplikationen im Herzkatheter, Entschleusung, Komplikationen nach Entschleusung) detaillierte Beschreibungen des Ablaufes und der einzelnen Untersuchungsschritte dokumentiert. Die Mitarbeiter werden vor Inkrafttreten der SOP und in dreimonatigen Abständen über die Inhalte der SOPs informiert und geschult, um eine zuverlässige und standardisierte Information aller – auch neuer – Mitarbeiter sicherzustellen.

Die neue SOP „Herzkatheter Vorbereitung“ wird den bereits in der Anästhesie gängigen „OP-Vorbereitungs-Checklisten“ angelehnt und auf die Bedürfnisse des Herzkatheters angepasst. Ziel dieser Liste ist eine zuverlässige und vollständige Erhebung der notwendigen Voruntersuchungen zu veranlassen und zu gewährleisten. Zusätzlich wird am Tag des Katheters die Mitgaben von Aufklärung, Akte und notwendigem Material (OP-Hemd, Wickel für den Kompressionsverband) abgefragt. Diese Checkliste dient einer Vervollständigung der für die Herzkatheteruntersuchung notwendigen Unterlagen, eine Modifikation des weiteren Untersuchungsablaufes aufgrund der abgefragten Inhalte ist nicht vorgesehen. Zur Sicherstellung einer vollständigen Abarbeitung der Liste ist ein Abzeichnen der erledigten Punkte

durch einen Arzt und durch ein Mitglied des Pflegepersonals notwendig, ohne vollständig abgearbeitete Liste ist eine Übergabe des Patienten an das Herzkatheter Personal nicht mehr möglich.

Die SOP für Komplikationen im Herzkatheter bezieht sich auf durch die Katheter Prozedur an sich hervorgerufene Komplikationen und deren standardisierte Behandlung. Sie dient als Handlungsleitfaden bei Zwischenfällen, um möglichst alle schwerwiegenden Komplikationen sicher beherrschen zu können. Diese im Detail zu erläutern würde den Rahmen dieser Arbeit sprengen, da sie jedoch Teil der im Herzkatheter zur Anwendung kommenden SOP sind, sollen sie nicht vollständig unerwähnt bleiben.

Die Erarbeitung sämtlicher SOP erfolgt in einzelnen Arbeitsgruppen. Meine Arbeitsgruppe der Angiologie, übernahm die Aufgabe für die SOP„Entschleusung“ (Entfernung der in das Gefäßsystem eingeführten Schleusensysteme) und „Gefäßkomplikationen nach HK“ (Handlungsleitfaden im Falle von Komplikationen im Zusammenhang mit der Gefäßpunktion). Infolge des hieraus resultierenden, für die gesamte Klinik standardisierten Vorgehens und der aufgrund der Struktur der SOP vollständigen Erfassung sämtlicher Gefäßkomplikationen über die Angiologie wird die Grundlage für eine wissenschaftliche Aufarbeitung der Daten gelegt. Über die strukturierte Erfassung der Komplikationen werden im weiteren Verlauf die Risiken für lokale Gefäßkomplikationen identifiziert, analysiert und anschließend die Prozesse entsprechend einem RM und QM modifiziert. Eine direkte Rückkopplung aufgrund der fortgeführten Erfassung mit weiteren Anpassungen entsprechend dem PDCA-Zyklus führt im Sinne des QM zu einer kontinuierlichen Prozessoptimierung. Das gesamte Konzept entspricht infolge Einbeziehung nicht nur des ärztlichen Personals sondern aller beteiligten Mitarbeiter mit Möglichkeit einer Einflussnahme auf Verfahrensabläufe einem TQM.

Erfassung

Identifizierung der Risiken

Basis für die Analysen sind die ab Januar 2006 erfassten Gefäßkomplikationen im Zusammenhang mit Herzkatheter Untersuchungen. Die Aufarbeitung dieser Ereignisse erfolgt auf mehreren Ebenen. Einerseits wird für jeden einzelnen Fall der Ablauf der Untersuchung von ihrer Vorbereitung bis zum Resultat der Komplikation aus Perspektive der Komplikation beleuchtet. Dies also im Sinne einer M&M-Konferenz für jede einzelne Gefäßkomplikation, um in diesem speziellen Fall eine (zu vermeidende Ursache) herausfiltern zu können. Darüber hinaus erfolgt eine strukturierte wissenschaftliche Analyse sämtlicher Gefäßkomplikationen, um über eine Prozessoptimierung eine Verbesserung der Qualität und Vermeidung von Fehlern zu erreichen.

In der Literatur ist eine Assoziation von Gefäßkomplikationen nach Herzkatheter Untersuchungen mit unterschiedlichen Risikofaktoren beschrieben.[36,37] So stehen diese im Zusammenhang mit akut nicht beeinflussbaren, teilweise patientenabhängigen Risikofaktoren wie: Alter, Geschlecht, BMI, Begleiterkrankungen (PAVK, Niereninsuffizienz),[38–40] Begleitmedikation (Antikoagulantien), Art des Eingriffes (HKU, PCI, Notfallintervention);[41–43] bedingt beeinflussbaren Faktoren wie: Blutdruck,[44] periinterventioneller Gabe von Antikoagulation (GP IIb/IIIa-Rezeptorblocker, Heparin),[44–46] Größe und Zahl der verwendeten Katheter Schleusen[47] und zu guter Letzt beeinflussbaren Risikofaktoren wie: Art des Zugangsweges[48] und Lokalisation der Punktionsstelle.[49]

Analyse der Risiken

Die Erhebung der tatsächlichen Komplikationsraten und ihre Verteilung innerhalb unserer Klinik, erfolgt ab Januar 2006 über einen Zeitraum von 12 Monaten mittels einer strukturierten Vor- und Nachuntersuchung sämtlicher

Patienten, die zu einer geplanten Herzkatheteruntersuchung aufgenommen werden, sowie einer Nachuntersuchung aller Notfallpatienten. Da diese Pateinten aufgrund des akuten Krankheitsbildes keine Zeitverzögerung bis zum Beginn der Katheteruntersuchung durch Voruntersuchungen erfahren sollen, werden sie lediglich nach der Katheteruntersuchung auf das Vorliegen einer Komplikation untersucht. Eventuell im Vorfeld zu erfassende Risikofaktoren liegen bei den Notfallpatienten also nicht prospektiv vor. Die Resultate dieser Erhebung sind in Abbildung 2 dargestellt[50] und stimmen für die elektiven Katheteruntersuchungen und die elektiven Katheterinterventionen weitgehend mit den Resultaten der Literatur überein.[51] Überraschend sind jedoch die Resultate für die Notfallpatienten, welche sehr häufig nicht unerhebliche Sickerblutungen mit signifikantem Abfall des Hämoglobinwertes erleiden. Ursache hierfür ist vermutlich, dass die manuelle Kompression mit einer engeren Nachbeobachtung (andere Kontrollintervalle für manuell komprimierte Patienten im Vergleich zu Patienten mit arteriellen Verschlusssystemen) zu einer geringeren Anzahl an schweren Blutungskomplikationen führt, da bereits leichte Blutungen frühzeitig erfasst und gegengesteuert werden kann. Diese Schlussfolgerung ist nicht anhand der erhobenen Daten zu ziehen, da diese lediglich der Erhebung der Komplikationsraten diente und nicht auf eine vollständige Ursachenabklärung ausgelegt war. Eine retrospektive Aufarbeitung der Fälle (über Analysen im Rahmen von M&M-Konferenzen) führt jedoch zu diesem Schluss, diese Erkenntnisse wurden später im Rahmen der weiteren Prozessoptimierung umgesetzt.

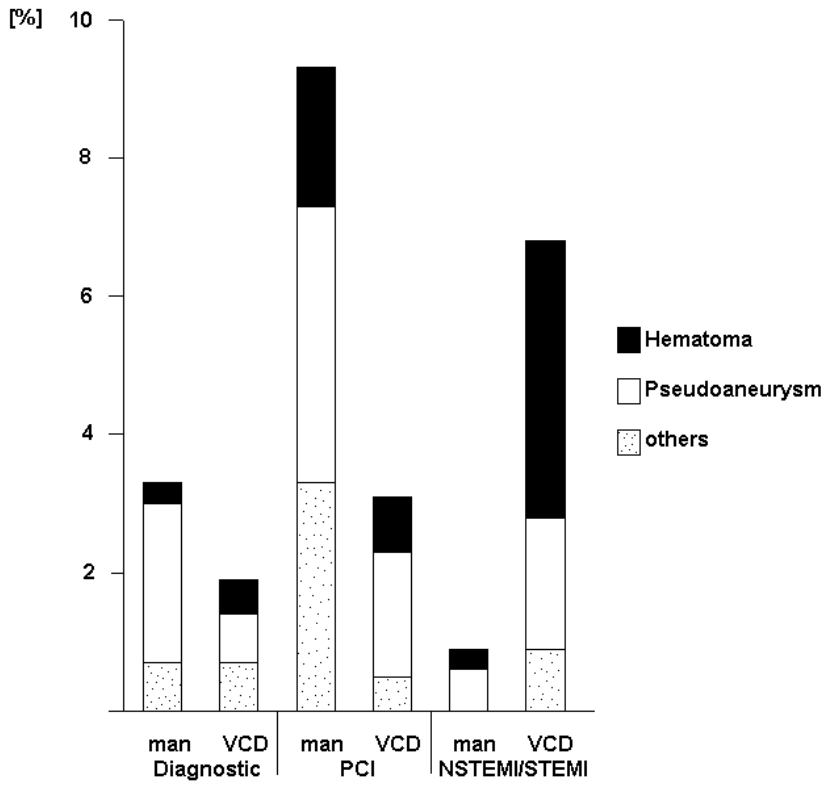

Abbildung 2: Rate an Gefäßkomplikationen in Anhängigkeit der Art des Eingriffes (Ordinate = Komplikationsrate in [%], man = manuelle Kompression, VCD = Verschlusssystem, Diagnostic = diagnostische Herzkatheteruntersuchung, PCI = Koronarintervention, NSTEMI = Nicht-ST-Hebungs-Myokardinfarkt, STEMI = ST-Hebungs-Myokardinfarkt, Hematoma = Hämatom, Pseudoaneurysm = Aneurysma spurium, others = sonstige Komplikation) (aus: Stegemann E, Clin Res Cardiol 2011)

In der Primäranalyse der Daten der ersten Erhebung kann darüber hinaus gezeigt werden, dass die Komplikationsraten durchaus von den einzelnen Untersuchern abhängen. Eine entsprechende Aufarbeitung dieser Resultate erfolgt in regelmäßigen Feedback-Runden wie später erläutert, eine Publikation findet aus Rücksichtnahme auf die einzelnen Mitarbeiter nicht statt, da eine vollkommene Anonymität nicht gewährleistet werden kann.

Ebenfalls in der Literatur vorbeschrieben ist eine erhöhte Komplikationsrate bei primärer Gefäßpunktion in einem suboptimalen Gefäßabschnitt.[44,49,52,53] Da die SOP „Entschleusung“ erstmals zwingend eine Angiografie der Punktionsstelle vorschreibt, kann diese auch erstmals sicher lokalisiert werden. Das überraschende Resultat ist, dass auch bei sehr erfahrenen Operateuren die

Punktion oftmals außerhalb des optimalen Bereiches ist, assoziiert mit erhöhten Komplikationsraten, ein weiterer Ansatzpunkt für die folgende Prozessoptimierung im Rahmen des QM.

Prozessoptimierung

Zwar besteht in der Klinik zu diesem Zeitpunkt kein „echtes“ CIRS-System für das Herzkatheter Labor, welches „Beinahe-Fehler“ oder „Fehler ohne schwerwiegende Folgen“ meldet und deren Vermeidung dann zu einer Reduktion von Schadensereignissen führt, eine Erfassung bestimmter Teilaspekte des Entschleusungsvorganges und der Komplikationen lässt aber Rückschlüsse auf „Beinahe-Fehler“ und „Fehler“ im Sinne eines CIRS zu. So ergeben sich Hinweise darauf, dass in einem nicht unerheblichen Prozentsatz die Gefäßpunktion in einem suboptimalen Bereich erfolgt und bei den Entschleusungsvorgängen selbst mehrfach identische Fehler gemacht wurden. Da die Art der Entschleusung unmittelbar vom gewählten Zugangsweg abhängt, liegt es somit nahe zunächst den Gefäßzugang zu optimieren und einem zweiten Schritt die Entschleusung in Angriff zu nehmen.

VI Resultate

Abbildung 3 stellt das erarbeitete Organigramm zu Beginn der hier beschriebenen Prozesse dar.

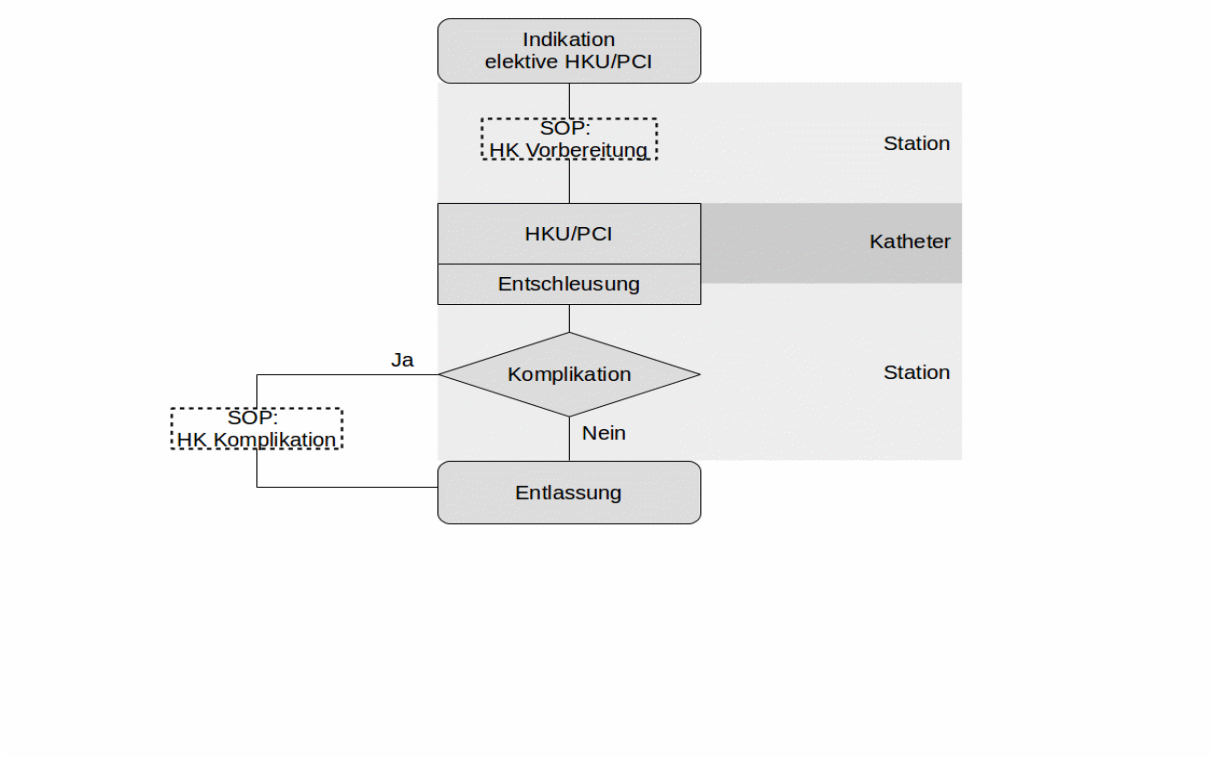

Abbildung 3: Ausgangsorganigramm „Punktionsstelle“ (HKU = Herzkatheteruntersuchung, PCI = Koronarintervention, SOP = Standard Operation Procedure, HK = Herzkatheter)

Unter diesem Konzept liegt eine Komplikationsrate von Katheter assoziierten Gefäßkomplikationen von 6,4% der Gesamtkomplikationen und 3,3% an schweren Komplikationen vor.

Die ermittelte Zahl an Gefäßkomplikationen liegt unter dem anhand von Literaturangaben im Durchschnitt erwarteten Wert und könnte somit zu einer Fortführung des eingesetzten und offenbar bewährten Konzeptes, stattdessen erfolgt jedoch eine strukturierte Aufarbeitung der Komplikationen, eine Erhebung der lokalen Risikofaktoren für Komplikationen und eine Überarbeitung

des Ablaufes der geplanten Herzkatheter Untersuchungen zur Vermeidung von Komplikationen.

Zugangswege

Da arterielle Punktionen im Rahmen von Herzkatheter Untersuchungen und peripheren Angiografien weltweit häufig durchgeführt werden und somit auch die Zahl der Komplikationen ein weltweit bekanntes Problem und deren Vermeidung überall erwünscht ist, verwundert es nicht, dass es hierzu zahlreiche Empfehlungen und Strategien gibt, diese zu vermeiden.[48,54–57] Leider sind die von zahlreichen Autoren propagierten Methoden entweder schwer zu erlernen oder sehr unhandlich in der Umsetzung, so dass sie keinen flächendeckenden Eingang in die tägliche klinische Routine genommen haben. Hier ist beispielsweise die seit Jahrzehnten bekannte fluoroskopisch gesteuerte Punktion der Leistenarterie zu nennen, welche mit viel Erfahrung zu einer verbesserten Trefferquote des Zielgefäßes führt.[54] Nachteil ist hier die sehr langsame Lernkurve und die erhöhte Strahlenbelastung für den Untersucher. Ein weiteres Beispiel ist die ultraschallgesteuerte Punktion der Leistenarterie, welche zusätzliche Gerätschaften (sterile Hüllen für den Ultraschallkopf) oder Hilfsmittel (Halte Arm) und zusätzliches Personal (Bedienung des Ultraschallgerätes) erfordern und die Punktionsdauer verlängern.[55] Wird dieses Verfahren täglich angewandt, gleichen sich die Punktionszeiten an, dies ist jedoch ein langer Prozess weshalb die meisten Labore hiervor zurückschrecken. Ausnahme sind einige wenige Zentren, dies sind aber überwiegend radiologische Zentren, mit einer - im Vergleich zu Herzkatheterlaboren - relativ geringen Patientenzahl und im Verhältnis längeren Prozedurdauern. Hier wirkt sich eine verlängerte Punktionszeit wenig auf die Gesamtlänge der Untersuchung aus und wird daher gut toleriert. In High-Volume-Katheterlaboren hingegen ist eine durchschnittliche Verlängerung jeder Prozedur um 5-10 Minuten nicht gut tolerabel, da die Katheterprozedur hierdurch überproportional verlängert wird.

Eine wichtige Voraussetzung für die Optimierung des Zugangsweges ist somit ein obligat außerhalb des Katheter Labors anzuwendendes Verfahren, welches für den Patienten nebenwirkungsfrei und für den Untersucher keinen Zwang für ein bestimmtes Punktionsverfahren beinhalten darf. Darüber hinaus sollte nach Möglichkeit keinerlei Zeitverzögerung im Herzkatheterlabor als Folge der Strategie entstehen.

Das nach eingehenden Abwägungen und Diskussionen als am geeignetsten ausgewählte und weiter verfolgte Verfahren, ist eine am Tag vor der geplanten Katheteruntersuchung durchgeführte klinische Untersuchung des Pulsstatus (Leiste, Kniekehle, Fußpulse) ergänzt durch eine Ultraschalluntersuchung der Leistenarterie mit simultaner Erhebung des Dopplerfrequenzspektrums zur Erfassung vorgeschalteter, hochgradiger Stenosen.[58] Im Rahmen dieser Untersuchung wird die Größe der Leistenarterie erfasst, wichtige Voraussetzung für die spätere Verwendung des eingesetzten arteriellen Verschlusssystems, welches einen Gefäßdurchmesser von mindestens 6mm fordert. Die zweite wichtige Information ist das Detektieren von atherosklerotischen Plaques im Punktionsbereich sowohl an der Vorder- als auch an der Hinterwand der Arterie. Dies hat sowohl für die Auswahl der Punktionsstelle (evtl. Wechsel auf die gegenüberliegende Seite bei Plaque an der Vorderseite des Gefäßes) als auch auf die Punktionsart (weniger steil bei dorsalem Plaque) bzw. auf die Art des Verschlusses (kein Verschlusssystem bei ventralem Plaque) Konsequenzen. Als dritte Information aus der Untersuchung lässt sich die tatsächliche Höhe der Gabelung der Arteria femoralis communis in die A femoralis superficialis und die A profunda femoris lokalisieren. Diese Lokalisation ist für eine korrekte Punktion unerlässlich und oftmals aufgrund anatomisch variabler Gegebenheiten (vor allem Adipositas) klinisch nicht ganz einfach einzuschätzen, da die entsprechenden Leitstrukturen vor allem bei Fettüberlagerung kaum mehr erkennbar sind; zusätzlich gibt es in nicht unerheblicher Zahl physiologische Varianten mit hoher und tiefer Bifurkation. Alle aufgezählten Informationen der Untersuchung werden mittels Markerstiften direkt auf der Haut der Patienten dokumentiert und sind somit am Folgetag für den Untersucher ohne weitere Zeitverzögerung oder

Einsichtnahme von zusätzlichen Untersuchungsbefunden vorliegend (Abbildung 4).

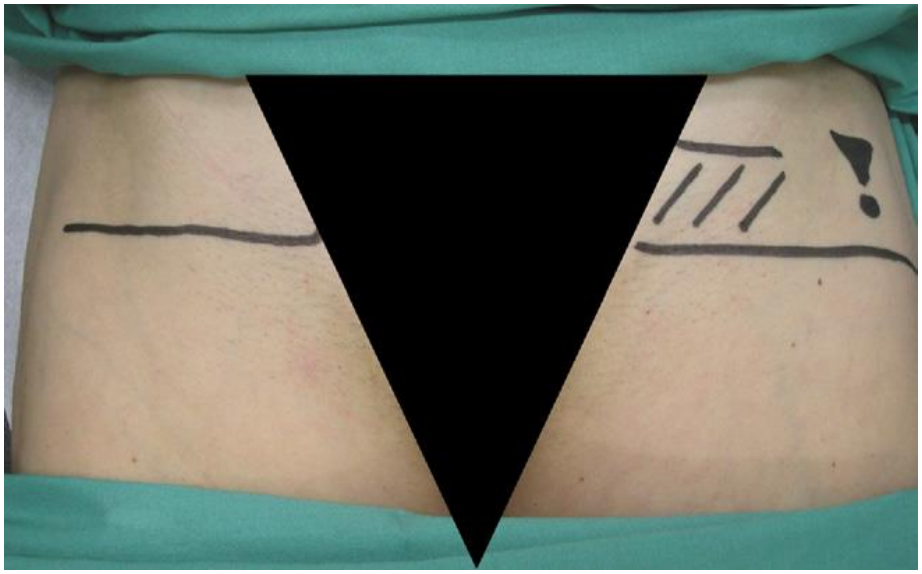

Abbildung 4: Beispiel für eine präinterventionelle Hautmarkierung: Markierung der Femoralisbifurkation (horizontale Linie), eines ventralen Plaques (schraffierte Fläche) sowie eines dorsalen Plaques (Ausrufezeichen) (aus: Stegemann E, AJC 2011)

Zu guter Letzt ergeben sich bei verändertem Dopplerfrequenzspektrum Hinweise auf hochgradige Stenosen oder Verschlüsse der Beckenetage, in diesen Fällen wird die entsprechende Leiste als „unbrauchbar“ mit einem „X“ markiert und langwierige Punktionsversuche beziehungsweise komplexe Passagen von stenosierten Beckenarterien im Vorfeld vermieden.

Überprüfung (Check)

Das einfache und von medizinischem Hilfspersonal nach kurzer Einarbeitung zuverlässig durchzuführende Ultraschallverfahren führt nachweislich zu einer signifikanten Erhöhung der optimalen Punktionslokalisation im Bereich der Leistenarterie und zu einer signifikanten Senkung der relevanten Komplikationen (Abbildung 5).

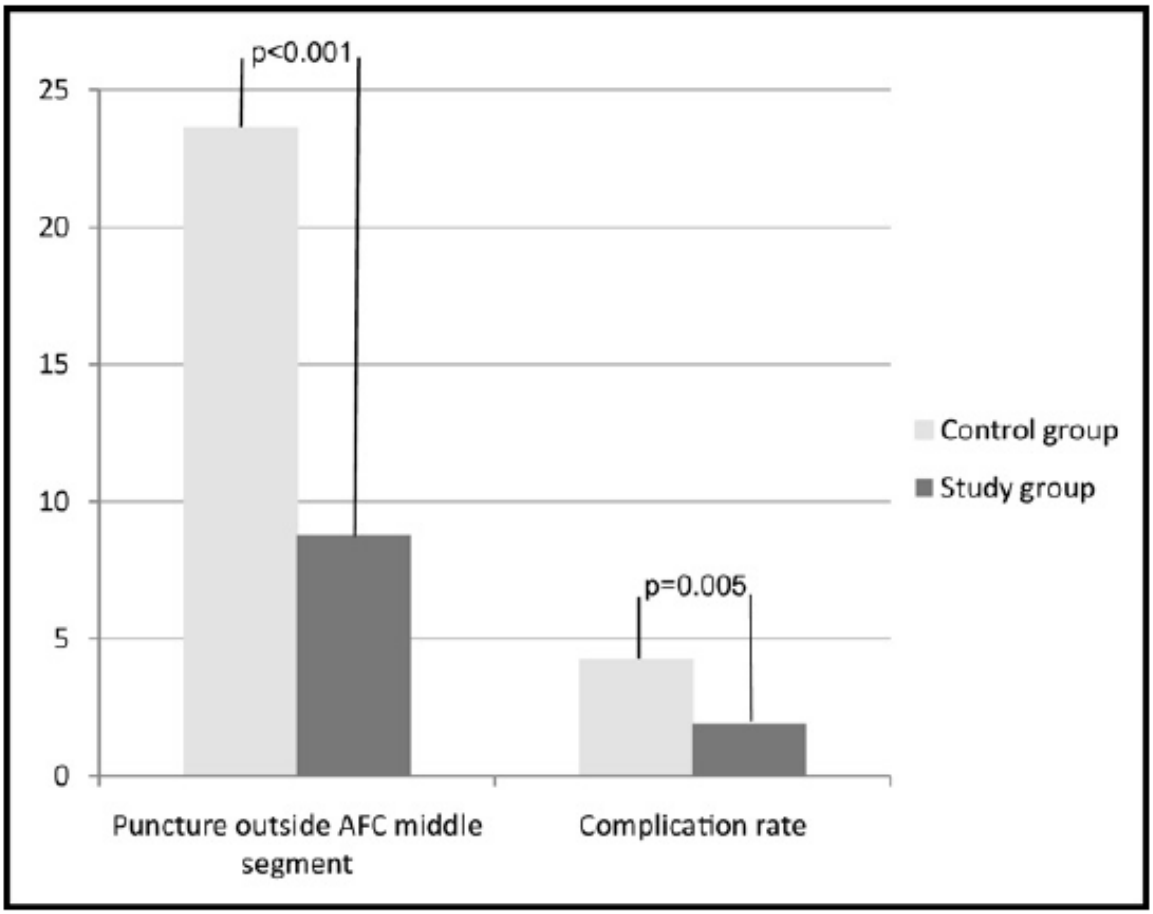

Abbildung 5: Einfluss von präinterventionellem Ultraschall auf die Lokalisation der Punktion und der Komplikationsrate (Ordinate [%] der Eingriffe, AFC = Arteria femoralis communis) (aus: Stegemann E, AJC 2011)

Es erfolgt umgehend die Umsetzung in der täglichen klinischen Routine und eine Einarbeitung in den Ablauf der Routinekatheteruntersuchung im Sinne des „Act“ im PDCA-Zyklus. Das modifizierte Organigramm ist in Abbildung 6 dargestellt.

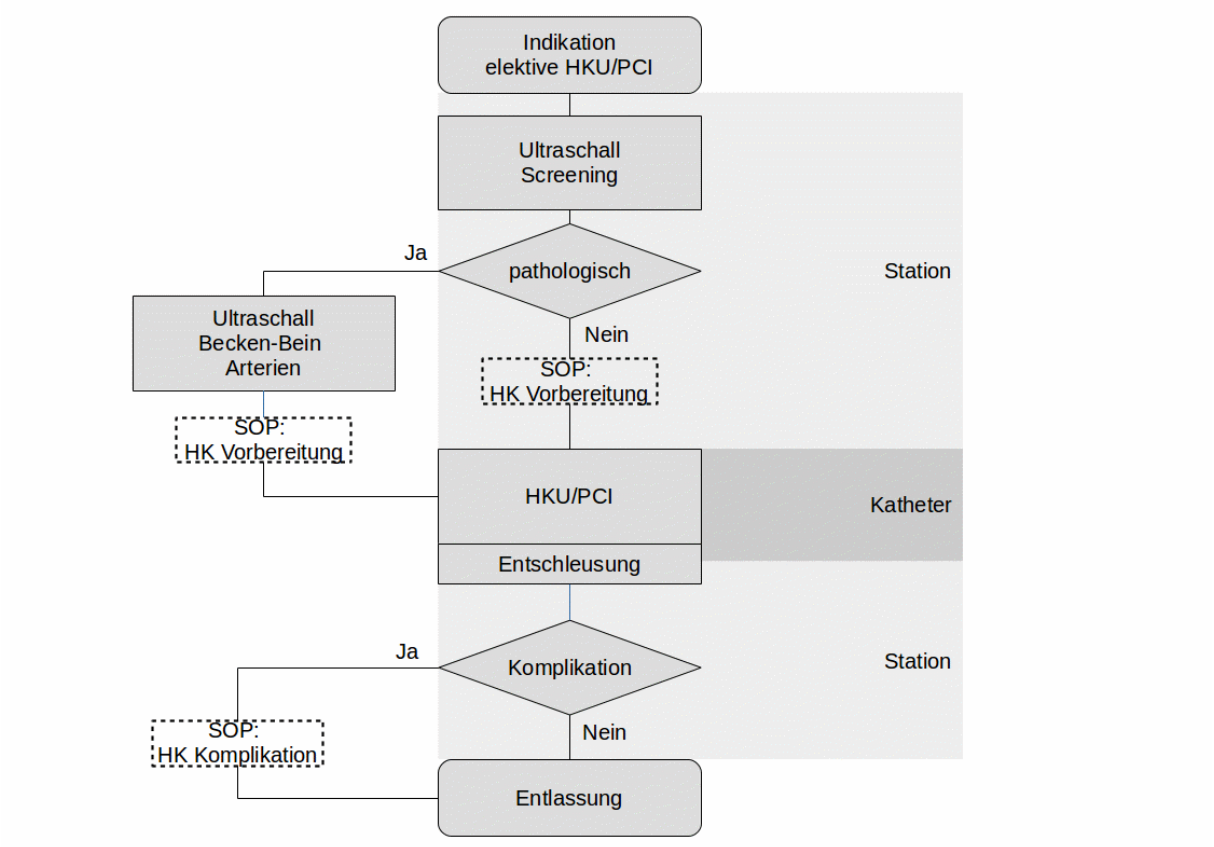

Abbildung 6: Organigramm „Punktionsstelle“ nach erster Modifikation (HKU = Herzkatheteruntersuchung, PCI = Koronarintervention, SOP = Standard Operation Procedure, HK = Herzkatheter)

Als „Nebenprodukt“ wird ein weiterer Zyklus im QM begonnen. Die durch die Sonografie der Leiste im Vorfeld der Katheteruntersuchung miterfasste PAVK ist ein unabhängiger Risikofaktor für Gefäßkomplikationen im Rahmen von arteriellen Punktionen.[39] Entsprechend detektierte Patienten werden im weiteren QM über eine Anpassung des RM (s. dort) in eine höhere Risikoklasse eingestuft und anschließend anderen Behandlungspfaden zugeführt.

Entschleusung

Als nächster Schritt zur Reduktion der Gefäßkomplikationen erfolgt eine Auswertung der Entschleusung nach Herzkatheteruntersuchung und in der Folge deren Umstrukturierung. In den Analysen ist besonders auffällig, dass die auf der Station nach Intervention entschleusten Patienten eine im Verhältnis hohe Komplikationsrate haben, welche aufgrund der Prädiktoren nicht in diesem Ausmaß zu erwarten ist. Retrospektiv analysiert kann kein ganz sicherer Grund hierfür gefunden werden, vermutlich ist es jedoch der enorme Zeitdruck unter dem zunehmend gearbeitet wird und der in minimaler Zeit maximale Effizienz fordert. Diametral zu den Komplikationsraten bei manueller Entschleusung, die bei deutlich längerer Kompression drastisch abnehmen.[59,60] Es ist anzunehmen, dass Zeitdruck zu einer Risiko-Nutzen-Abwägung mit einer konsekutiv minimalistischen Kompressionsdauer geführt hat, auf Kosten von etwas mehr lokalen Komplikationen.

Die erhobenen Befunde führen erneut zu einer Änderung im Ablauf der Herzkatheter Untersuchungen, dieses Mal im Anschluss an die eigentliche Angiografie. Zum einen erfolgt die Entschleusung nicht mehr regelhaft auf Station, sondern im Herzkatheter Labor. Hierfür wird ein spezieller Bereich abgetrennt, in dem die Patienten für einen Zeitraum von mindestens 60 Minuten zusätzlich an einem Monitor überwacht werden und somit Herzfrequenz- und Blutdruckänderungen, die Frühzeichen einer auftretenden Komplikation sein können, unmittelbar erfasst werden. Zum anderen wird die Entschleusung entsprechend „strengen“ Schemata mit im Verhältnis langen Kompressionszeiten vorgeschrieben und durch medizinisches Hilfspersonal (unter Aufsicht von Ärzten) durchgeführt.

<u>Überprüfung (Check)</u>

Dieses Verfahren wird auf Gleichwertigkeit mit Entschleusung durch ärztliches Personal untersucht, um eine qualitativ hochwertige Versorgung der Patienten weiterhin sicherzustellen.[61] Ergebnis dieser Verfahrensweise ist, dass die Zahl der mit der Entschleusung in Zusammenhang zu bringenden Komplikationen nicht zunimmt, sondern tendenziell sogar abnimmt. Dies ist während des

Beobachtungszeitraumes statistisch (gerade) nicht signifikant jedoch ein eindeutiger Trend. Das Ziel der Untersuchung, eine Nichtunterlegenheit der Entschleusung durch nichtärztliches Personal zu zeigen, wird jedoch sicher erreicht. Es erfolgt umgehend eine Umsetzung mittels erneuter Anpassung des Organigramms wie in Abbildung 7 dargestellt.

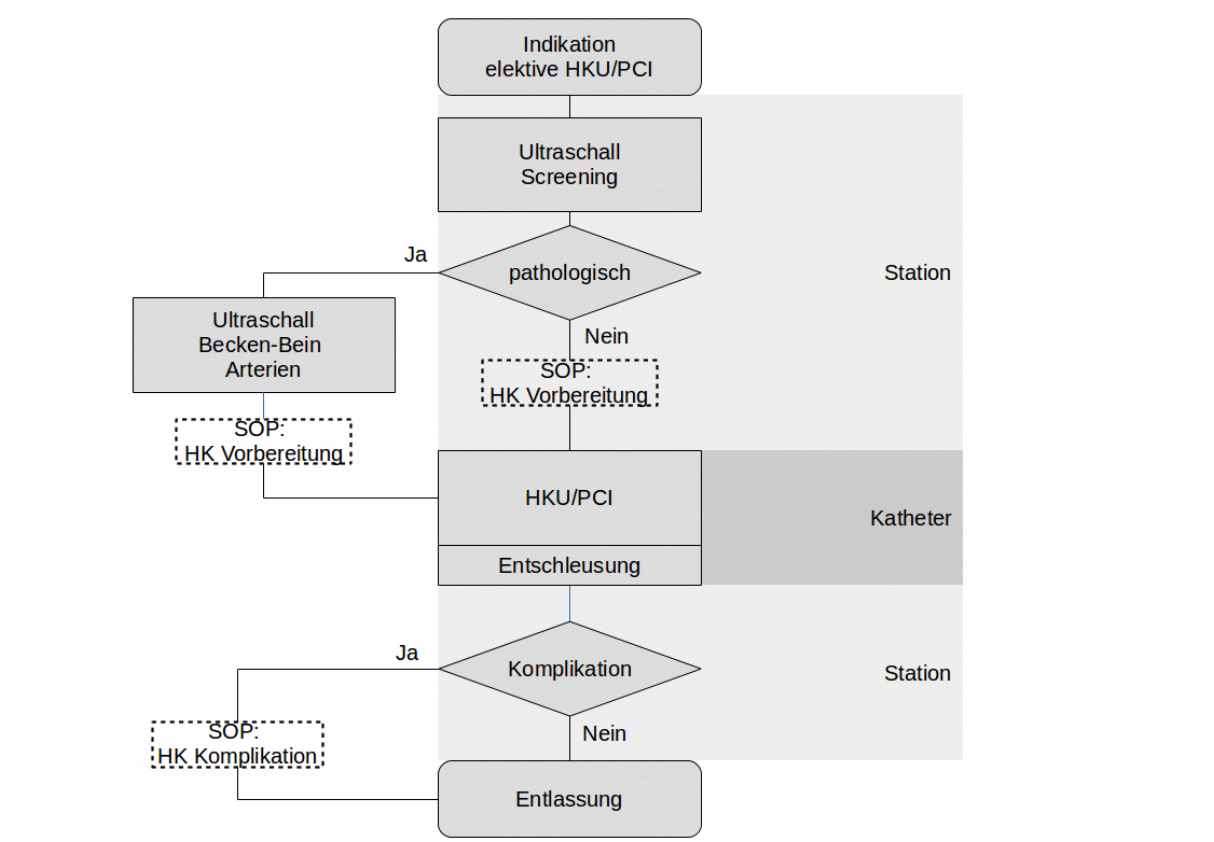

Abbildung 7: Organigramm „Punktionsstelle“ nach zweiter Modifikation (HKU = Herzkatheteruntersuchung, PCI = Koronarintervention, SOP = Standard Operation Procedure, HK = Herzkatheter)

Zusätzlich entsteht eine sehr hohe Mitarbeiterzufriedenheit, da das ärztliche Personal von der Aufgabe des eher unbeliebten „Schleusenziehens“ befreit ist und das medizinische Hilfspersonal nun aktiven Anteil am Katheter Verfahren hat und sich besser integriert und deutlich aufgewertet fühlt. Im Sinne des

TQM[34] erfolgt ergänzt durch die Feedbackrunden somit eine volle Integration von nichtärztlichen Mitarbeitern in den Gesamtprozess, welche zuvor lediglich als Ausführende beteiligt waren. Nicht zuletzt haben die Patienten durch das längere Verweilen im Herzkatheter in der frühen Phase nach Schleusenentfernung eine bessere Überwachung als auf der Normalstation, einige geringfügige Blutungen werden in diesem Rahmen während des Überwachungszeitraumes erfasst und unmittelbar behandelt.

Punktionstechniken

Zur Optimierung der Abläufe und Rückmeldung über weitergeleitete Informationen werden regelmäßige Feedbackrunden in dreimonatigen Abständen etabliert. Teilnehmer dieser Runden sind der Klinikdirektor, die Oberärzte der Klinik, die im Herzkatheter Labor eingesetzten Assistenzärzte und die Leitung der Pflegekräfte und der MTA im Herzkatheter Labor. Im Rahmen dieser Besprechungen werden sowohl die Struktur der Abläufe als auch personenimmanente Probleme angesprochen, entsprechend einer Kombination aus M&M-Konferenz und Vorstellung von CIRS-Meldungen.

Zu Beginn der Feedbackrunden erfolgt zunächst die anonymisierte Vorstellung der Komplikationen mit Aufarbeitung der Komplikationsursachen. Zusätzlich erhält jeder Operateur eine Übersicht über seine eigenen Komplikationen und einen Vergleich seiner Komplikationsraten mit dem Durchschnitt. Eine Offenlegung sämtlicher Komplikationen in nicht-anonymisierter Form ist im Rahmen der ersten Sitzungen nicht erwünscht, da man sich bezüglich der Konsequenzen nicht sicher ist. Im weiteren Verlauf der regelmäßig stattfindenden Besprechungen kommt es dann jedoch unter den Kollegen zu einem spontanen Austausch über die jeweiligen Komplikationsraten und -arten, so dass schließlich eine komplette Offenlegung der Daten innerhalb der Gruppe der Operateure gewünscht wird.

So wird beispielsweise offenbar, dass einige Komplikationen fast spezifisch für einzelne Untersucher sind. Es gibt einige Untersucher, die für (fast) alle AV-Fisteln im Gesamtkollektiv verantwortlich sind, dies ist zwar statistisch bezogen auf die Gesamtkomplikationen nicht signifikant, für die einzelnen Operateure jedoch durchaus relevant. Im Rahmen einer weiteren Ursachenanalyse zeigt sich, dass die Untersucher vollständig unterschiedliche Punktionstechniken verwenden.

Überprüfung (Check)

Nach Erlernen einer anderen Punktionstechnik durch Umschulung und kollegiale Unterstützung, ist diese Art der Komplikation fast nicht mehr nachweisbar, auch bei den zuvor „auffälligen“ Untersuchern. Da die Gesamtzahl der Komplikationen für eine wissenschaftliche Analyse einer Änderung der Strategie leider zu klein ist (man hätte nur für diese eine Komplikation >50.000 Katheteruntersuchungen analysieren müssen), kann dies leider nicht in einer prospektiven Studie belegt werden.

Technische Fertigkeiten

Eine weitere Auffälligkeit ist, dass zwei Untersucher überzufällig häufig „Versager“ bei den verwendeten Verschlusssystemen zeigen. Hier liegt ein einfacher Anwendungsfehler vor, der sich im Rahmen der Feedbackrunden herauskristallisiert und der relativ einfach behoben werden kann, indem die Kollegen eine erneute Unterweisung erhalten. Da dies vollständig auf Augenhöhe geschieht und kein Kollege als „schlecht“, „Versager“ oder „Verursacher von Fehlern“ gebrandmarkt wird, resultiert nicht nur eine deutliche Verminderung der Fehlerquote sondern darüber hinaus eine Verstärkung des Teams als funktionierendes Ganzes. Ohne untersucherspezifische Auswertungen wäre dies nie aufgefallen, die extrem offene und kollegiale Zusammenarbeit hat hier zusätzlich zu einer Verbesserung der Qualität geführt.

Patientenabhängige Risiken

Im Rahmen der Voruntersuchung am Vortag der Intervention werden auf Wunsch der Operateure die für Gefäßkomplikationen bekannten und auch im eigenen Kollektiv eruierten Risikofaktoren abgefragt und in der Akte hinterlegt. Die zugrundeliegende Idee ist, dass der Patient im Falle von mehr als drei vorhandenen Risikofaktoren als Hochrisikopatient geführt und der Operateur mit besonderer Vorsicht die Untersuchung durchführt (und evtl. komplikationsträchtigere Interventionen vermeidet soweit medizinisch vertretbar). Im Rahmen der Feedbackrunden fällt dann auf, dass eine zuverlässige Information an den Operateur nicht zu 100% sichergestellt ist, wenn das Ergebnis des Risikoscreenings ausschließlich in der Akte vermerkt wird.

Im Verlauf wird daher zusätzlich auf dem Bein des Patienten das Kürzel „HR“ vermerkt („high-risk“) und der Operateur durch die assistierende Schwester, welche den Patienten vor der Untersuchung ohne Abdeckung durch OP-Tücher sieht, über den Vermerk informiert, was zu einer nahezu 100%igen Informationsweitergabe führt. Später noch werden die Risikoscores im Rahmen der Katheter Anmeldung über den Computer abgefragt und weiter verfeinert (Implementierung international anerkannter Risikoscores wie der HASBLED-Blutungsscore und Scores zum Abschätzen des Interventionsrisikos[62–64]), dies ist jedoch nicht mehr Bestandteil dieser Untersuchung.

Zusätzlich wird im Rahmen der Risikostratefizierung vor Herzkatheteruntersuchung die Niereninsuffizienz als ein Risikofaktor für mögliche Gefäßkomplikationen gesichert, vergleichbare Hinweise finden sich auch in der Literatur.[38,40] Der genaue pathophysiologische Hintergrund ist noch nicht geklärt, vermutet wird, dass es aufgrund der Niereninsuffizienz und der folgenden Störung im Calcium-Phosphat-Haushalt zu einer Wandversteifung der Arterien mit dann schlechterer Hämostase kommt. Diese wird teilweise durch eine Kontraktion der glatten Muskulatur in der Gefäßwand verursacht und könnte durch eine Kalzifikation der Tunica media der Arterie erschwert werden.[45] Eine Strategie zur Vermeidung von Gefäßkomplikationen bei

Patienten mit Niereninsuffizienz konnte im Rahmen der vorliegenden Untersuchungen nicht erarbeitet werden, die Idee einer nephroprotektiven Untersuchung der Patienten zur Vermeidung einer weiteren Verschlechterung der Nierenfunktion war jedoch Grundlage einer weiteren Untersuchung. Als mögliches Kontrast Agens bei Patienten mit einer peripheren arteriellen Verschlusserkrankung besteht die Möglichkeit des Einsatzes von Kohlendioxid,[65,66] es wird jedoch mit verlängerten Untersuchungszeiten und höherer Strahlenbelastung für Patienten und Personal in Zusammenhang gebracht.[67] Im eigenen Patientengut zeigt sich, dass eine Angiografie der Beinarterien mit Kohlendioxid als Kontrastmittel für Patienten mit einer eingeschränkten Nierenfunktion sicher und ohne vermehrte Strahlenbelastung oder Erhöhung der Komplikationsrate bei gleichen Prozedurerfolgen machbar war.[68] Eine direkte Umsetzung der Strategie mittels regelmäßigen Einsatzes bei Risikopatienten erfolgte unmittelbar im Anschluss an diese Resultate.

Interdisziplinäre Zusammenarbeit

Die (teilweise) Übernahme von Arbeitsschritten durch medizinisches Hilfspersonal (Screening durch MTA, Entschleusung durch Rettungsassistenten/Intensivpfleger) ist ebenfalls Thema der Feedbackrunden. Dank TQM, mit Möglichkeit der Einflussnahme aller Beteiligten unabhängig von ihrer Stellung in der Klinik, mit dem gemeinsamen Ziel einer bestmöglichen Qualität, werden während des Prozesses auch Teilbereiche verändert, die nicht primär im Fokus des ärztlichen Führungspersonals waren. So wird beispielsweise im Bereich der Herzkatheter Zone, in der die Entschleusungen durchgeführt werden, eine einfach zu bedienende Klingelanlage installiert. Darüber hinaus werden zur sicheren Einhaltung der notwendigen Kompressionszeit einfache Stoppuhren angeschafft, die am Ende der Prozedur auf die in Tabellen ablesbare minimal erforderliche Kompressionszeit eingestellt werden.

Im Rahmen des umfassenden QM wird das gesamte Personal in die Feedbackrunden eingeschlossen und erhält entsprechend Rückkopplung zwecks Erarbeitung weiterer Optimierungsprozesse. Diese Maßnahmen sind zunächst ungewohnt, zumal die ursprünglich bestehenden Hierarchien deutlich abgeflacht werden, sind jedoch aufgrund des Erfolges und der spürbar erhöhten Zufriedenheit des gesamten Personals überzeugend.

VII Diskussion

Total Quality Management kann auch in der Medizin erfolgreich umgesetzt werden, wie in der vorliegenden Arbeit anhand einer umfassenden und kontinuierlichen Anpassung von Prozessabläufen im Umfeld einer High-Volume-Kathetereinheit an einem universitären Zentrum in Deutschland unter Einbeziehung des gesamten Personals dargelegt.

Die rasante Weiterentwicklung der medizinischen Wissenschaft und Technik hat in den vergangenen Jahrzehnten zu einer enormen Erhöhung der Komplexität in der klinischen Medizin geführt. Vor allem in interventionellen Fächern wie der Kardiologie hat eine Einführung immer aufwendigerer Verfahren stattgefunden.[69,70] Als Folge werden zunehmend langwierige und durch multiple Faktoren beeinflussbare Prozeduren durchgeführt, welche eine perfekte Abstimmung zwischen Organisationsabläufen, räumlichen Gegebenheiten, Material, Operateur und Assistenzpersonal zwingend verlangen.[71,72] Durch eine zunehmende Alterung der Bevölkerung und hierdurch bedingt auch der zu behandelnden Patienten entsteht eine weitere Dimension der Verkomplizierung, da durch zahlreiche Begleiterkrankungen und Wechselwirkungen derselben aufeinander und auf Behandlungsverfahren ein hochkomplexes, zunehmend störanfälliges System entstanden ist.[73–75] Eine Überwachung eines solchen Systems inklusive Risikomanagement und ständiger Qualitätskontrolle ist zur Sicherung aller Beteiligten notwendig und teilweise inzwischen auch gesetzlich vorgeschrieben.[26]

Im Spezialfall der Kardiologie stellt das Herzkatheter Labor das zentrale Element der interventionellen Kardiologie dar, somit liegt es nahe als erstes die mit ihm im Zusammenhang stehenden Prozesse in den Fokus des Interesses zu stellen. Es gibt seit Jahrzehnten zahlreiche Ansätze die Räumlichkeiten,[35,71] die Prozesse,[72,76] die Bildqualität,[77] die Strahlenbelastung[78] sowie das Komplikations- und Risikomanagement[79] zu optimieren. Nachdem primär im Sinne einer Qualitätssicherung beziehungsweise darauf aufbauend einer Qualitätskontrolle vorgegangen wird, entwickelt sich in den 90er Jahren des letzten Jahrhunderts das QM mit implementiertem RM.

So erfolgt zunächst die Erarbeitung von Standard-Operation-Procedure (SOP) für Routineabläufe und die Kontrolle in Form von Checklisten, welche die Basis der Qualitätssicherung darstellen. Im Rahmen der Qualitätskontrolle werden dann zur Aufarbeitung von Fehlerursachen und zur Analyse von Schadensfällen Morbiditäts- und Mortalitätsanalysen (M&M-Konferenzen) eingeführt. Da im Rahmen der Analysen offensichtlich wird, dass ein wesentlich größerer Teil an Fehlern bemerkt und im System abgefangen wird, man diese zur Verbesserung der Sicherheit aber in ihrem Entstehen verhindern will, wird das Critical Incident Reporting System (CIRS) entwickelt. Dieses erlaubt eine anonyme Meldung von Fehlern und Beinahe-Fehlern und in der weiteren Aufarbeitung dann ein Anpassen der SOP. Meldesysteme werden zunehmend gefordert, seit Juli 2016 sind Fehlermeldungen in Deutschland erstattungsfähig, wenn sie den Anforderungen des Gemeinsamen Bundesausschusses entsprechen.[80] Diese Maßnahmen beinhalten allerdings alle lediglich die Merkmale einer Qualitätssicherung und -kontrolle, eine Erweiterung im Sinne eines QM setzt sich in der Medizin nur sehr langsam durch. Ursache hierfür könnten die in der Medizin teilweise noch weiterhin bestehenden ausgeprägten Hierarchien sein, die ein QM im Sinne eines TQM nicht erlauben.[81] Noch Ende der 90er Jahre des 20. Jahrhunderts zeigt sich die Medizin sehr weit von „echter“ Teamarbeit und angemessener Selbsteinschätzung entfernt.[82] In einer Umfrage schätzen sich 70% der befragten Chirurgen als effektiv trotz Müdigkeit ein, 82% sind der Überzeugung, dass private Probleme das Berufliche nicht beeinflussen und 24% bewerten das Wort des Vorgesetzten als unumstößlich und auf keinen Fall hinterfragbar. Zunehmende Aufklärung in den Reihen der Mediziner und ein eindeutiger Ansporn durch erfolgreiches QM in der Industrie[11] führen jedoch auch in der Medizin allmählich zu einem langsamen Umdenken und der festen Verankerung von SOP, M&M-Konferenzen und CIRS sowie einer Entwicklung von QM-Systemen.[2,15–17,29]

Voraussetzung für die in dieser Arbeit vorgestellten Prozesse ist eine Umsetzung des QM „von oben nach unten“. Die weit verbreiteten Ängste vor Offenlegung von Fehlern, ehrlichen Risikoanalysen und transparentem Umgang mit problematischen Situationen können nur dann erfolgreich abgebaut werden,

wenn ein Austausch auf Augenhöhe stattfindet.[14] TQM kann daher nicht eingefordert werden, es entsteht und wird gelebt indem alle Mitarbeiter ein gemeinsames Ziel haben und verfolgen,[12,81] so auch in der vorliegenden Arbeit.

Ausgangspunkt der hier vorgestellten Prozesse ist ein „Standardablaufplan“ für Patienten, die eine Untersuchung im Herzkatheterabor erhalten sollen (Abbildung 3). Grundlage sind die aktuellen Empfehlungen der Fachgesellschaften,[35] die langjährige klinische Erfahrung der beteiligten Mitarbeiter, sowie eine gemeinsame Überlegung an welchen Stellen in der eigenen Klinik kritische Probleme auftreten könnten.

Als erster Schritt werden die Risikofaktoren für Gefäßkomplikationen erfasst und den Operateuren zur Kenntnis gebracht. Zum einen in der Form, dass überhaupt darüber aufgeklärt wird, dass es Risikofaktoren für Komplikationen gibt, zum anderen durch individuelles Hervorheben von Risikopatienten, um eine höhere Aufmerksamkeit beim Untersucher zu erreichen. So kann dieser nicht zwingend notwendige, eventuell mit einem höheren Risiko behaftete Prozeduren, vermeiden, soweit dies medizinisch vertretbar ist. Vergleichbare Rückkopplungsverfahren sind aus der Qualitätskontrolle bekannt und führen bereits alleine eingesetzt zu einer Verringerung von unerwünschten Ereignissen.[30] Besonderes Augenmerk wird dann im Sinne eines QM auf die Punktionstechnik gerichtet. Umfragen zu Beginn der Maßnahmen ergeben, dass die erfahrenen Operateure „gefühlt“ in 95% den optimalen Bereich der Leistenarterie punktieren. Aufgrund der neu eingeführten SOP erfolgt zwingend eine Kontrastmitteldarstellung der Leistenregion mit konsekutiv objektivierbarer Lokalisationsmöglichkeit der tatsächlichen Punktionsstelle für jede Untersuchung. Überraschenderweise, nicht zuletzt für die langjährig im Katheter Labor tätigen Kollegen, liegt die Zahl der optimalen Punktionen jedoch bei lediglich 77%, durchaus im Rahmen der publizierten Resultate von Kollegen,[48] subjektiv allerdings höchst unbefriedigend. Verschiedene Strategien zur Vermeidung falscher Punktionen werden im Folgenden anhand von Literaturrecherchen[48,55,56] und Diskussionen erarbeitet und gegeneinander abgewogen. Ein nicht unerheblicher Teil der der Literatur zu entnehmenden Verfahren ist jedoch in Angiosuiten erarbeitet, in denen Interventionen an

peripheren Gefäßen durchgeführt werden; da die Gesamtabläufe der Bereiche doch zu unterschiedlich sind, sind diese nicht vollständig in die Kardiologie übertragbar. Entsprechend dem QM-Prozess wird dann schließlich entsprechend Deming[83] eine „Ultraschalluntersuchung der Leistenregion mit Markierung der Femoralisbifurkation“ als umsetzbare Verbesserung untersucht und nach Nachweis einer signifikanten Reduktion der Gefäßkomplikationen als Routineparameter in den Ablauf eingefügt. Hierdurch wird eine relative Risikoreduktion von Gefäßkomplikationen um 45% erreicht. Der Ablauf der elektiven Untersuchungen wird in Folge durch eine Ergänzung durch ein verbindliches Ultraschallscreening entsprechend geändert (Abbildung 6). Bereits ein einziger Durchlauf des PDCA- (Deming-) Zyklus zeigt positive Resultate im Sinne verminderter Komplikationsraten, als Nebeneffekt verringern sich die Hemmschwellen zur Meldung von Problemen und Fehlern, da diese vollständig erfragt und erfasst werden und anstelle Repressalien ein konstruktives Feedback stattfindet. Dieser Effekt wird in der entsprechenden Literatur beschrieben, aber regelmäßig und immer wieder in Frage gestellt.[30] Der sich allmählich etablierende Prozess des TQM als zu akzeptierender und schrittweise zu erlernender Prozess aller Mitarbeiter[34] war im gesamten Team deutlich spürbar.

Nächster Ansatzpunkt der Prozessoptimierung ist die Entfernung der Katheter Schleusen nach der Untersuchung, im Folgenden auch „Entschleusung“ genannt. Diese kann mittels manueller Kompression erfolgen, ein häufig langwieriges und bei Ärzten nicht sehr beliebtes Verfahren, bei dem man die arterielle Punktionsstelle bis zum Erreichen der Hämostase manuell komprimiert und anschließend einen Kompressionsverband anlegt.[47,84] Dieses Verfahren wird seit den 90er Jahren zunehmend von speziellen Verschlusssystemen abgelöst, die die Punktionsstelle schnell und zuverlässig verschließen und rasch zu einer recht zuverlässigen Blutstillung führen.[85] Diese Alternative erfreute sich relativ rasch zunehmender Beliebtheit, zumal nachweislich die Rate an schweren Gefäßkomplikationen bei Verwendung dieser Systeme geringer ist.[36,37,43] Da jedoch zum einen diese Systeme bei bestimmten Konstellationen nicht einsetzbar sind (zum Beispiel bei Punktion im

Bereich eines atherosklerotischen Plaques oder bei zu geringen Gefäßkalibern) und zum anderen nicht jeder Eingriff zwingend mit einem solchen System versorgt werden muss (bei kleinen Kathetern müsste die Punktionsstelle zum Einsatz eines solchen Systems erst einmal vergrößert werden, da diese erst ab einer bestimmten Größe erhältlich sind), wird weiterhin eine nicht unerhebliche Zahl an Entschleusungen mittels manueller Kompression durchgeführt. Hierbei führt nachweislich eine verlängerte Kompression zu einer Verminderung von Komplikationsraten.[47,51] Im Gegensatz zu anderen Ländern ist es in Deutschland unüblich, dass nichtärztliches Personal die Aufgabe der manuellen Kompression übernimmt, die in der Literatur beschriebenen positiven Erfahrungen aus dem europäischen Ausland, insbesondere aus Großbritannien, führt zur Ausarbeitung eines neuen Entschleusungskonzeptes.[86,87] Erstmals werden nun auch nichtärztliche Mitarbeiter in Zielerreichung und Feedbackrunden im Sinne einer Modifikation des QM in Richtung TQM einbezogen.[2] Das neue Entschleusungsverfahren führt zu einer weiteren Modifizierung der Untersuchungs- und Überwachungsabläufe. Diese werden in den kommenden Jahren nicht weiter verändert, dafür aber andere Teilbereiche rund um die Katheterverfahren modifiziert (s. Aussichten).

Ähnliche Ansätze finden sich im amerikanischen Gesundheitssystem, wo über jahrzehntelange Routine im Fehlermanagement und der kontinuierlichen Prozessoptimierung der Gesamterfolg des Teams größer wird als die Summe der Einzelerfolge.[29,88] Immer wieder wird jedoch darauf hingewiesen, dass diese Resultate nicht Ergebnis einer einfachen Schulung mit sofortigem Erfolg, sondern Resultat jahrelanger Prozesse und regelmäßig durchlaufenen Anpassungen mit einem motivierten Team sind.[12,14] Hierbei entstehen in der Regel aus den in Angriff genommenen Teilaspekten neue Ideen für Verbesserungen, welche dann in eigenen PDCA-Zyklen in Angriff genommen werden können.[13] Das TQM ist somit ein ständig in Bewegung befindliches Verfahren mit multiplen parallel laufenden Prozessen auf den verschiedensten Ebenen. Diese Erfahrung haben wir auch gemacht, die entsprechenden Ansätze und Ideen für weitere Projekte sind unter „Aussichten“ aufgeführt.

VIII Zusammenfassung

Während eines Zeitraumes von drei Jahren wird mittels Einsatz von Risiko- und Qualitätsmanagement in einer universitären High-Volume-Herzkatheter Einheit eine Reduktion von zugangsassoziierten lokalen Gefäßkomplikationen von 6,4% auf <1% erreicht. Daten belegen, dass diese Komplikationen nicht nur zu einer Verlängerung des Krankenhausaufenthaltes führen, sondern tatsächlich das Langzeitüberleben der betroffenen Patienten verkürzen.[89] Ob im Gegenschluss eine Verminderung dieser Komplikationen zu einem verlängerten Langzeitüberleben führt ist zwar nicht nachgewiesen, wird aber allgemein angenommen.[90] Darüber hinaus können durch das konsequente Qualitätsmanagement alleine in unserem Herzkatheterlabor jährlich knapp 300 Patienten vor derartigen Komplikationen geschützt werden.

In Deutschland werden pro Jahr etwa 800.000 Herzkatheter Untersuchungen durchgeführt, davon weiterhin etwa 70% über den transfemoralen Zugangsweg. Bei einer Komplikationsrate von etwa 4% über alle Eingriffe kommt es also zu etwa 22.400 schweren Komplikationen als Folge von Herzkatheter Untersuchungen. Würde das hier vorgestellte Verfahren flächendeckend angewendet, wäre eine Vermeidung von Gefäßkomplikationen im Rahmen von Herzkatheter Untersuchungen in knapp 17.000 Fällen jährlich möglich.

IX Limitationen

Bei dem beschriebenen Katheter Labor handelt es sich um ein universitäres High-Volume-Labor mit großem Personalvolumen, eine Übertragung der Resultate auf sämtliche Katheter Labore ist somit nicht uneingeschränkt möglich. Neben dem sehr hohen Patientenumsatz besitzen die Operateure eine weit überdurchschnittliche Expertise und sind aufgrund ihrer Stellung in einem universitären Lehrbetrieb selbst an Innovation interessiert und teilweise in die Entwicklung neuer Verfahren involviert. Eine solche Personalsituation macht die Umsetzung eines innovativen Projektes leichter, zumal kleinere Labore deutlich länger benötigen, um die notwendigen Rückkopplungsschleifen zu durchlaufen. Sehr ungewöhnlich ist auch die enge und wenig hierarchische Zusammenarbeit des ärztlichen und Pflegepersonals im beschriebenen Labor, eine immanente Voraussetzung des TQM.

X Aussichten

Eine in dieser Arbeit nicht vorgestellte Möglichkeit der Reduktion von lokalen Komplikationen bei Herzkatheter Untersuchungen ist die Wahl eines alternativen Zugangsweges über die Arteria radialis.[91,92] Da das Gefäß sehr oberflächlich liegt werden Blutungen fast unmittelbar erfasst und führen nur extrem selten zu einer Ausbildung großer Hämatome oder einem schweren Verlust an Hämoglobin. Dies hat ein nachweislich verbessertes Langzeitüberleben der Patienten zur Folge, weshalb dieses Verfahren vor allem in Notfallsituationen, wo es sich als besonders vorteilhaft erwiesen hat, empfohlen wird.[92–94] Ein Nachteil des Verfahrens ist jedoch, dass es in nicht unerheblicher Zahl zu einem vollständigen Verschluss des Gefäßes kommt.[95] Ob eine Katheteruntersuchung über die verhältnismäßig kleine Radialarterie für die Patienten Langzeitfolgen hat, ist noch nicht umfassend wissenschaftlich aufgearbeitet,[96,97] zumal das Verfahren noch nicht ausreichend lange flächendeckend eingesetzt wird, um ausreichend Material zur Auswertung vorliegen zu haben. In der Arbeitsgruppe der Angiologie wurde der alternative Zugangsweg der Radialarterie für Herzkatheter Untersuchungen im Rahmen von Risikoreduktion von Gefäßkomplikationen untersucht. Als ein unerwünschter Nebeneffekt zeigte sich eine vaskuläre Dysfunktion der Brachialarterie, welche noch 24 Stunden nach der eigentlichen Herzkatheteruntersuchung nachweisbar war.[98] Mit höherer Anzahl erfolgter Katheter Wechsel und bei Rauchern zeigte sich eine im Vergleich deutlich verlängerte Funktionseinschränkung des Endothels. Zusätzlich konnte eine Zunahme der Wandsteifigkeit und der Wanddicke nach transradialer Herzkatheteruntersuchung gezeigt werden.[99] Diese waren unter Einfluss von Nikotin unmittelbar im Zusammenhang mit der Herzkatheteruntersuchung verstärkt.[100] Ob eine Möglichkeit der Verminderung oder Vermeidung entsprechender Veränderungen beispielsweise durch Gabe gefäßprotektiver Substanzen besteht, ist aktuell im Fokus weiterer wissenschaftlicher Projekte.

XI Verwendete Abkürzungen

CIRS	Critical Incident Reporting System
CRM	Clinical Risk Management
HLM	Healthcare Lean Management
M&M	Morbidity & Mortality
MTA	Medizinisch Technische(r) Assistent(in)
PAVK	Periphere Arterielle VerschlussKrankheit
QM	Qualitätsmanagement
RM	Risikomanagement
SOP	Standard Operating Procedure
TQM	Total Quality Management

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Stegemann E, Lee KM, Schauerte P, Rajan V, Stegemann B. Microvascular tissue perfusion using Laser Doppler Techique for the differentiation of hemodynamically stable and unstable arrhythmia. DGA 2011

Stegemann E, Sansone R, Stegemann B, Kelm M, Heiss C. Structural and mechanical radial artery adaption after transradial cardiac catheterization. DGA 2012

Stegemann E, Lee KM, Rajan V, Stegemann B, Kelm M. Laser Doppler Tissue Perfusion Monitoring for the Differentiation of hemodynamically stable and unstable tachycardia. DGK 2012.

Stegemann E, Busch L, Stegemann B, Lauer T, Heiss C, Kelm M. Implementation and Evaluation of a structured training program for sheath removal after cardiac catheterization procedures by paramedics. DGK 2012.

Stegemann E, Sansone R, Stegemann B, Kelm M, Heiss C. Validation of high resolution ultrasound measurements of Intima Media thickness for the Assessment of structural remodeling follwoing transradial cardiac catheterization. DEGUM 2012.

Stegemann E, Sansone R, Özaslan G, Westenfeld R, Heiss C. Structural and functional changes of the vessel wall after arterial injury are boosted by current smoking. DEGUM 2013.

Stegemann E, Lauer T, Stegemann B, Hoffmann R, Kelm M, Heiss C. Interdepartmental cooperation in access-site management – verifiable persistent benefit for patients. DGA 2014

Stegemann E, Tegtmeier C, Sansone R, Richter A, Stegemann B, Westenfeld R, Kelm M.
Carbon dioxide-aided angiography decreases contrast volume and prevents kidney injury in peripheral vascular interventions. DGA 2015

XV Curriculum vitae

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Beruflicher Werdegang

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XVI Danksagung

Mein ganz besonderer Dank gilt meinem Mentor und unermüdlichen „Gasgeber“ Herrn **Malte Kelm**. Mit seiner unbeschreiblichen Art hat er mich in meinem Unterfangen nicht nur unentwegt unterstützt, sondern auch immer wieder ermutigt trotz zahlreicher, scheinbar unüberwindbarer Hürden nicht aufzugeben. DANKE!

Sämtliche statistischen Arbeiten und zahlreiche kritischen Anmerkungen und Korrekturen habe ich meinem lieben Mann **Berthold Stegemann** zu verdanken. Sein Perfektionismus hat mich manches Mal schier verzweifeln lassen. Hätte er mich jedoch nicht sowieso schon vor Jahren mit dieser gesunden Skepsis erobert, wäre es ihm spätestens in den letzten zehn Jahren gelungen.

Meine Kinder **Ole, Emil und Nele Stegemann** haben mir bei der Erstellung der Arbeit definitiv nicht aktiv geholfen, vermutlich haben sie deren Entstehung und Erstellung eher drastisch in die Länge gezogen. Sie haben mich jedoch vor allem in den Jahren 2009 bis 2015 unterstützt, indem sie regelmäßig bewusst auf gemeinsame Unternehmungen und Urlaube verzichtet haben, damit ich meine wissenschaftlichen Arbeiten durchführen konnte.

Frau **Brigitte Eichstädt** danke ich, dass sie mich unermüdlich ermutigt hat das Vorhaben Habilitation nicht an den Nagel zu hängen. Oftmals war der Spagat zwischen Wollen und Können schwer zu schaffen, ohne ihre ständigen Ermutigungen hätte ich es wahrscheinlich nicht bis zum Ende geschafft.

Schließlich gilt mein Dank meinem Kollegen **Christian Heiss**. Gemeinsam haben wir jahrelang mit sehr viel Freude und Spaß klinisch und wissenschaftlich zusammen gearbeitet. Im Prinzip haben wir uns so perfekt ergänzt, dass wir als Team quasi unschlagbar waren.