Risk Predictors of Retroperitoneal Hemorrhage Following Percutaneous Coronary Intervention

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Retroperitoneal hemorrhage (RPH) is a potentially catastrophic complication after percutaneous coronary intervention (PCI). Previous studies identified female gender, body surface area, and high arterial puncture location as independent risk factors for RPH. There have been conflicting reports regarding the association with vascular closure devices (VCDs). Chronic renal insufficiency (CRI) and diabetes mellitus have been associated with both peripheral vascular disease and vascular access-site complications. The putative association of VCDs, CRI, and diabetes mellitus with RPH in the contemporary PCI era was investigated. A total of 3,062 consecutive patients undergoing 3,482 PCIs at Brigham and Women's Hospital from January 2005 to April 2007 were evaluated for the study. All 3,311 patients with femoral angiography underwent hand-caliper–based quantitative vascular analysis and were included in this analysis. Multivariate analysis was performed using a backwards selection algorithm, and a propensity adjustment was developed to control for possible confounding variables regarding VCD use. The incidence of RPH was 0.49% (17 of 3,482 patients). After multivariate and propensity analyses, covariates that significantly influenced the risk of RPH were CRI, glycoprotein IIb/IIIa inhibitors, and high arterial puncture ($p \leq 0.007$). VCD use was not independently associated with the development of RPH ($p = 0.74$). In conclusion, this large prospective cohort study identified CRI, but not VCD use, as an independent predictor for RPH and peripheral vascular disease. **(Am J Cardiol 2008;102:1473–1476)**

Retroperitoneal hemorrhage (RPH) is a potentially fatal vascular access complication of invasive coronary procedures performed using the transfemoral route and is associated with significant morbidity and mortality.[1–6] Vascular closure device (VCD) use has grown significantly during the last decade, and there have been conflicting reports regarding their association with RPH.[3,4,7–10] In this study, we evaluated all femoral angiograms obtained from January 2005 to April 2007 at our institution for patients undergoing percutaneous coronary interventions (PCIs) with quantitative vascular analysis to explore as many risk factors as possible regarding the development of RPH. The objective of this study was to determine the possible association of RPH with VCD use, history of chronic renal insufficiency (CRI), diabetes mellitus, peripheral vascular disease (PVD), puncture location, and access site anatomy assessed using quantitative vascular analysis. Propensity adjustment was performed to control for possible confounding variables regarding VCD use.

Methods

All 3,062 patients undergoing 3,482 PCIs using the transfemoral approach at Brigham and Women's Hospital, Boston, Massachusetts, from January 1, 2005, to April 27, 2007, were enrolled in this prospective cohort evaluation. Patients with clinical symptoms of RPH underwent aggressive hemodynamic stabilization followed by computed tomography during the next days. Clinical, demographic, procedural, and in-hospital outcomes were collected using a prospective cardiac catheterization database.[11] CRI was defined as preprocedural documented creatinine ≥ 2.0 mg/dl.[11] Off-hour cases were defined as cases started between 8 P.M. and 7 A.M. All variables were also analyzed for the prespecified subset of patients with high arterial puncture. All patients gave informed consent for the diagnostic and interventional coronary catheterization. The study was reviewed and approved by the hospital's institutional review board.

According to our institutional policy, all patients undergoing PCI had a standardized femoral angiogram obtained in an ipsilateral oblique view without significant cranial or caudal angulation. Trained angiographic reviewers blinded to clinical patient-related data reviewed all angiograms at the Brigham and Women's Hospital. Using the contrast-filled femoral sheath as the calibration source, hand-caliper–based quantitative angiographic analyses were performed. The femoral angiographic findings studied included the artery punctured, size of this artery, site of arterial puncture relative to the bifurcation, size of the common femoral artery at the site of the pelvic brim, and presence of PVD in major arteries, defined as visual stenosis $\geq 50\%$. The femoral head was divided in thirds from top to bottom. A puncture site at or above the upper third of the femoral head was defined as a "high stick location."

PCI procedures were performed according to the stan-

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dard American College of Cardiology/American Heart Association guidelines. All patients undergoing stent placement received aspirin and clopidogrel. Intraprocedural anticoagulation and antiplatelet therapy, including heparin, glycoprotein IIb/IIIa inhibitors (eptifibatide or abciximab), and bivalirudin, were used at the discretion of the performing operator. VCDs were used routinely on all patients undergoing PCI unless contraindicated. Contraindications to VCD deployment included ≥50% narrowing because of calcification or plaque in the punctured artery and diameter of punctured artery <4 mm. The VCDs used were Angioseal (St. Jude Medical, St. Paul, Minnesota), Starclose (Abbott Vascular, Redwood Shores, California), or Perclose Proglide (Abbott Vascular). Standard manual compression was used for patients not considered eligible for VCDs. Sheath removal was performed at an activated clotting time <160 ms when manual compression was used and immediately after the procedure for VCDs.

All statistical analyses were performed on an intention-to-treat basis using Stata Intercooled, version 8.0 (Stata Corp. LP, College Station, Texas). Chi-square test or Fisher's exact test was used as appropriate to compare categorical data, and 2-tailed unpaired Student's *t* test was used for continuous variables. A 2-sided $p < 0.05$ was considered statistically significant. A multivariable logistic regression model was developed to identify independent predictors of RPH using a backwards selection algorithm, and the final model incorporated covariates with consistent associations of $p < 0.10$. Odds ratios and 95% confidence intervals were calculated. The discriminatory power of the logistic regression models was measured using the area under the receiver-operating characteristic curve, and calibration was measured using Hosmer-Lemeshow C statistics.[12,13] Selection bias was controlled for by the regression adjustment method of propensity analysis described by D'Agostino.[14] The propensity score model was developed using multiple clinical factors, including operator, glycoprotein IIb/IIIa inhibitor use, patient gender and age, size of the punctured artery, and presence of PVD, venous access, and high arterial puncture. The predicted propensity score for each patient was subsequently incorporated as a continuous variable in the final multivariate logistic regression models. A prespecified subanalysis was performed on the population of patients with high stick location to assess the specific predictors of RPH in this high-risk patient subset.

Results

Baseline, procedural, and outcome data for 3,482 consecutive patients who underwent PCI were analyzed. Quantitative vascular analysis was performed on all 3,311 available femoral angiograms, representing >95% of all patients. Most of the 171 patient without available femoral angiograms for review were transferred to our institution with the vascular sheath in place and femoral angiograms obtained at the outside hospital. We identified 17 patients with diagnosed RPH, all confirmed using computed tomography, resulting in an overall incidence of 0.49%. The incidence decreased over time from 0.73% (12 of 1,637 patients) in 2005 to 0.33% (5 of 1,496 patients) in 2006, with no RPH case diagnosed in the first 4 months of 2007. Patients with RPH had a mortality rate of 12% compared with 1.3% for non-RPH patients ($p = 0.047$), and the hospital length of stay for these patients was 7.2 days compared with 2.6 days ($p < 0.001$). Thirteen of 17 patients with RPH required blood transfusions, with an average of 2.7 red blood cell concentrates.

Table 1
Univariate analysis: baseline and procedural characteristics

Variable	RPH		p Value
	Yes (n = 17)	No (n = 3,465)	
Age (yrs)	72.2 ± 11.9	66.7 ± 12.2	0.06
Women	9 (53%)	1,043 (30%)	0.08
Weight (kg)	77.3 ± 16.3	84.9 ± 19.0	0.10
Body surface area (m^2)	1.86 ± 0.21	1.96 ± 0.24	0.09
Diabetes	6 (35%)	1,038 (30%)	0.81
Renal insufficiency	5 (29%)	196 (6%)	<0.001
Creatinine (mg/dl)	2.11 ± 2.16	1.17 ± 0.92	<0.001
International normalized ratio ≥1.8	4 (24%)	73 (2%)	<0.001
PVD	3 (18%)	393 (11%)	0.61
Acute myocardial infarction	1 (6%)	201 (6%)	0.78
Cardiogenic shock	1 (6%)	68 (2%)	0.58
Emergent admission	9 (53%)	696 (20%)	0.006
Elective PCI	4 (24%)	1,119 (32%)	0.63
Urgent PCI	9 (53%)	1,863 (54%)	0.88
Emergent PCI	4 (24%)	458 (13%)	0.36
Salvage PCI	0 (0%)	25 (1%)	0.57
Arterial sheath >7 Fr	1 (6%)	167 (5%)	0.88
Venous sheath	7 (41%)	748 (22%)	0.11
Bivalirudin use	2 (12%)	827 (24%)	0.38
Glycoprotein IIb/IIIa use	13 (77%)	1,448 (42%)	0.005
Balloon pump use	1 (6%)	111 (3%)	0.85
No. of intervened coronaries	1.35 ± 0.49	1.14 ± 0.48	0.07
Procedure time (min)	93.3 ± 54.2	75.8 ± 40.3	0.08
Fluoroscopy time (min)	31.9 ± 21.8	24.5 ± 16.8	0.07
VCD use	14 (82%)	2,853 (82%)	0.77

Continous variables expressed as mean ± SD; other variables as absolute counts (percent) of patients.

VCDs were deployed in 82% of patients and included Angioseal in 59%, Starclose in 5%, and Perclose in 18%. One of the 63 patients with an unsuccessful VCD deployment developed RPH, without a significant difference compared with the entire population ($p = 0.34$). Patients without an available angiogram and patients with PVD were more likely to undergo manual compression ($p < 0.001$) without association with RPH ($p \geq 0.94$). Angioseal was used in 14 of 17 patients with RPH, with 1 failure and subsequent manual compression; Perclose was used in 1 patient; and 2 patients had manual compression, a distribution without statistical difference compared with the entire population or non-RPH patients. RRs for all patients and those with a high stick location to develop RPH with the use of Angioseal were 1.39 and 1.32, with 95% confidence intervals of 0.96 to 1.63 and 0.90 to 1.56, respectively. The corrected absolute size of the punctured artery and its ratio to the external iliac artery were similar for patients with RPH (6.1 mm and 0.9) and non-RPH patients (6.6 mm and 0.9; $p > 0.27$).

History of CRI and higher preprocedural creatinine were observed more often in patients with RPH compared with

Table 2
Analysis of all available 3,311 femoral angiograms

Variable	RPH		p Value
	Yes (n = 17)	No (n = 3,294)	
High stick location	6 (35%)	400 (12%)	0.004
Artery punctured (mm)	6.1 ± 2.0	6.6 ± 1.9	0.28
External iliac artery (mm)	6.9 ± 2.6	7.4 ± 2.1	0.33
Punctured artery			
Common femoral artery	12 (71%)	2,840 (86%)	0.15
Profunda femoris artery	0 (0%)	115 (4%)	0.91
Superficial femoral artery	0 (0%)	265 (8%)	0.49
External iliac artery	5 (29%)	74 (2%)	<0.001
Presence of PVD			
Common femoral artery	1 (6%)	150 (5%)	0.91
Profunda femoris artery	1 (6%)	130 (4%)	0.99
Superficial femoral artery	1 (6%)	141 (4%)	0.95
Branch artery	1 (6%)	19 (1%)	0.20
External iliac artery	1 (6%)	66 (2%)	0.59
Any ileofemoral PVD	1 (6%)	303 (9%)	0.95

Artery punctured and external iliac artery expressed as mean ± SD. Other variables expressed as absolute counts (percent) of patients.

Table 3
Univariate, multivariate, and propensity analyses of RPH risk factors for all cases (n = 3,482)

Variable	Univariate		Multivariate		Propensity	
	RR	p Value	RR	p Value	RR	p Value
Age (yrs)	1.06	0.08	1.04	0.05		
Renal insufficiency	6.88	<0.001	7.73	<0.001	7.38	0.001
Glycoprotein IIb/IIIa use	4.56	0.005	6.13	0.002	6.16	0.002
High stick	4.18	0.01	3.94	0.01	4.42	0.007
VCD use	1.28	0.98	1.15	0.84	1.27	0.74

the entire cohort (p <0.001; Table 1). Patients with CRI developed more often postprocedural acute renal failure compared with all patients after a similar amount of contrast dye (p = 0.014). The mortality rate of patients with CRI was 3% compared with 1.4% for the entire population (p = 0.17), the percentage requiring blood transfusion was 7% compared with 2% (p <0.001), and hospitalization length was 4.9 days compared with 2.6 days (p <0.001).

Glycoprotein IIb/IIIa inhibitors were used significantly more often in patients who developed RPH (p = 0.005). Analysis of femoral angiograms identified high stick location (p = 0.003) and puncture of the external iliac artery (p <0.001) to be associated with the development of RPH (Table 2). Angiographic presence and location of PVD were not associated with RPH, but PVD was associated with CRI and VCD use (p <0.001).

Significant covariates associated with RPH in the final multivariate logistic regression analysis model were history of CRI (p <0.001), use of glycoprotein IIb/IIIa inhibitors (p = 0.002), and presence of a high stick location (p = 0.01; Table 3). Importantly, VCD use was not independently associated with the development of RPH in this model. The ability of the model to assess the association of the studied variables with RPH was good, with adequate goodness of fit (area under the curve 0.74, Hosmer-Lemeshow C statistic = 0.06).

Table 4
Univariate, multivariate, and propensity analyses of RPH risk factors for patients with high arterial puncture (n = 412)

Variable	Univariate		Multivariate		Propensity	
	RR	p Value	RR	p Value	RR	p Value
Women	19.43	0.08	10.71	0.053	10.8	0.052
Renal insufficiency	25.87	0.13	7.31	0.03	7.16	0.04
Balloon pump use	12.51	0.08	12.14	0.06	16.54	0.14
VCD use	2.34	0.93	NA	0.97	NA	0.97
Procedure duration	1.03	0.23	1.02	0.056	1.02	0.056

A propensity adjustment analysis identified history of CRI (p = 0.001), use of glycoprotein IIb/IIIa inhibitors (p = 0.002), and the presence of a high stick location (p = 0.007) as independent predictors for the development of RPH (Table 3). VCDs and diabetes mellitus were not significantly associated with the development of RPH in the final model (p ≥0.74). Overall, the ability of the model to assess the association of the studied variables with RPH was good, with adequate goodness of fit (area under the curve 0.73, Hosmer-Lemeshow C value = 0.22).

The corresponding analyses were also performed separately for the prespecified subset of 412 patients with high stick location. Analysis of variables from Table 1 comparing patients with a high stick location with the rest of the studied population identified more women (p <0.001), emergent admissions (p = 0.04), longer procedure times (p <0.001), and more frequent use of Angioseal (p = 0.04), venous sheaths (p = 0.004), and bivalirudin (p = 0.03) in the high stick group, whereas a balloon pump was used less often (p <0.001). There was no association between VCDs and RPH (p = 0.74) in patients with a high stick location despite more frequent use of VCDs (91%) compared with the other patients (81%; p <0.001). After multivariable logistic regression analysis and propensity analysis for the high puncture cases, only CRI was significantly associated with RPH (p = 0.04; Table 4). The ability of the model to predict the association of the studied variables with RPH in patients with a high stick was good (area under the curve 0.84), but the model did not achieve adequate goodness of fit, with a Hosmer-Lemeshow C value of 0.01, either with or without use of VCD propensity score.

This analysis identified use of glycoprotein IIb/IIIa inhibitors, high femoral arterial puncture, and CRI as independent predictors of RPH. No significant association was found between use of VCDs and the development of RPH in the entire population or in the prespecified analysis for patients with high puncture.

Discussion

VCDs have become popular for achieving hemostasis of the femoral arteriotomy site after PCI procedures because of advantages in patient comfort and early ambulation.[1,2] However, there have been conflicting published reports regarding the safety and efficacy of the various types of available VCDs.[3,4,9,10] In a recently published large series

of patients with RPH after PCI from Stanford University Medical Center, use of VCDs was not associated with increased risk of RPH.[3] Conversely, a study from Cleveland Clinic reported a greater incidence of RPH after deployment of VCDs, whereas only a small percentage of femoral angiograms were evaluated using a case-control method.[4] A recent large review from our institution reported a lower risk-adjusted access-site complication rate for VCDs compared with manual compression after assessing 12,937 consecutive patients undergoing diagnostic and interventional catheterization.[10] A recently published meta-analysis including 37 trials with approximately 4,000 patients showed no difference regarding the efficacy and safety of closure devices compared with manual compression.[15] In a different meta-analysis including 30 randomized, case-control, and cohort studies with 37,066 patients, Angioseal use showed a similar incidence of access-related complications compared with mechanical compression after PCI.[16]

CRI was associated with increased in-hospital mortality and major bleeding after PCI.[17,18] Advanced CRI, defined as creatinine $\geq$2.0 mg/dl, was an independent risk factor for RPH in our study for the entire population and for patients with a high stick after multivariate and propensity analyses and was associated with worse in-hospital outcome. In a previous study, patients with RPH had a lower creatinine clearance compared with the matched control group without reaching statistical significance ($p = 0.24$) comparing 26 patients with RPH and 50 matched controls.[3]

High femoral arterial puncture was consistently found to be the strongest predictor of RPH development.[3,4,15,16] Our standardized evaluation of all femoral angiograms allowed the identification of all high sticks and the specific risk factors, including female gender, longer procedures, emergent admissions with urgent puncture, and previous placement of a venous sheath with possible change of reference points. Using multivariate and propensity adjustment analyses, our study found that VCDs were not associated with increased risk of RPH in the entire population or the prespecified subgroup with high stick location despite more frequent use of VCDs, specifically Angioseal, in this group. The RR to develop RPH was numerically higher for VCDs without statistical significance in the high stick group (RR 2.34, $p = 0.926$). In this study, 82% of the entire patient cohort had VCD deployments, a rate significantly higher than in previous studies.[3,4] Our center's experience with >20,000 VCD deployments, routine femoral angiograms, and weight-based anticoagulation regimens could explain the lower complication rates with VCDs compared with previous reports.

The present retrospective cohort study had limitations because it represented a nonrandomized review of prospectively acquired data regarding vascular complications in a single large academic center with extensive experience with VCDs. The RPH incidence decreased significantly during the studied period, possibly because of a Hawthorne effect, when studied events are observed less frequently than previously reported.[19] The frequency of complications, including the incidence of RPH, was low, thereby limiting the ability to identify associations with candidate predictors.

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