Balloon Angioplasty and Stenting of Branch Pulmonary Arteries

Adverse Events and Procedural Characteristics: Results of a Multi-Institutional Registry

Ralf J. Holzer, MD, MSc; Kimberlee Gauvreau, ScD; Jacqueline Kreutzer, MD; Ryan Leahy, MD; Joshua Murphy, MD; James E. Lock, MD; John P. Cheatham, MD; Lisa Bergersen, MD, MPH

Background—Pulmonary artery (PA) balloon angioplasty and/or stenting (PA rehabilitation) is one of the most common procedures performed in the cardiac catheterization laboratory, but comprehensive and consistently reported data on procedure-related adverse events (AE) are scarce.

Methods and Results—Data were prospectively collected using a multicenter registry (Congenital Cardiac Catheterization Project on Outcomes). All cases that included balloon angioplasty and/or stent implantation in a proximal or lobar PA position were included. Multivariate analysis was used to evaluate for independent predictors of AE and need for early reintervention. Between February 2007 and December 2009, 8 institutions submitted details on 1315 procedures with a PA intervention. An AE was documented in 22% with a high severity (level 3 to 5) AE in 10% of cases. Types of AE included vascular/cardiac trauma (19%), technical AE (15%), arrhythmias (15%), hemodynamic AE (14%), bleeding via endotracheal tube/reperfusion injury (12%), and other AE (24%). AE were classified as not preventable in 50%, possibly preventable in 41%, and preventable in 9%. By multivariate analysis, independent risk factors for level 3 to 5 AE were presence of $\geq$2 indicators of hemodynamic vulnerability, age below 1 month, use of cutting balloons, and operator experience of $<$10 years. Reintervention during the study period occurred in 22% of patients undergoing PA rehabilitation.

Conclusions—PA rehabilitation is associated with a 10% incidence of high-level severity AE. Hemodynamic vulnerability, young age, use of cutting balloons, and lower operator experience were significant independent risk factors for procedure-related AE. **(*Circ Cardiovasc Interv*. 2011;4:287-296.)**

Key Words: congenital heart disease ■ pulmonary artery stenosis ■ cardiac catheterization ■ adverse events

Pulmonary artery (PA) balloon angioplasty and/or stenting (PA rehabilitation), is one of the most common procedures performed in cardiac catheterization laboratories treating congenital heart disease. Within the Congenital Cardiac Catheterization Project on Outcomes (C3PO) registry,[1] on average 11% of cardiac catheterization included PA rehabilitation, ranging between 6% and 17% among participating institutions. However, comprehensive and consistently reported data on procedure-related adverse events (AE) is scarce with most studies reporting small, retrospective, single-center experiences with $<$50 patients. The incidence of serious AE has been reported to be $<$5% for PA stenting[2–7] and 4% to 18% for balloon angioplasty,[1,8–10] but inconsistent definitions and capture of AE make it nearly impossible to compare event rates among institutions or conduct a meta-analysis on adverse outcomes for balloon angioplasty and/or stenting of PA.

Clinical Perspective on p 296

Bergersen et al[1] recently reported on the C3PO a multicenter registry prospectively collecting outcome data on a variety of cardiac catheterization procedures.[1] The present study was designed to explore the results of balloon angioplasty and/or stent placement in branch PAs and identify predictors of AE in this population.

Methods

Data were prospectively collected using the C3PO, a multi-institutional interventional registry with 8 participating institutions. Details pertaining to registry design have recently been reported by Bergersen et al.[1] All physicians participating in the C3PO registry reviewed and approved the content of this manuscript.

Received December 28, 2010; accepted March 22, 2011.

From The Heart Center, Nationwide Children's Hospital, Columbus OH (R.J.H., J.P.C.); the Department of Cardiology, Children's Hospital Boston, Boston MA (K.G., J.E.L., L.B.); Children's Hospital of Pittsburgh, Pittsburgh, PA (J.K.); The Heart Institute, Division of Cardiology, Cincinnati Children's Hospital, Cincinnati, OH (R.L.); and the Division of Cardiology, Washington University, St Louis School of Medicine, St Louis, MO (J.M.).

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/cgi/content/full/CIRCINTERVENTIONS.110.961029/DC1.

Correspondence to Ralf J. Holzer, MD, MSc, FSCAI, Cardiac Catheterization and Interventional Therapy, Cardiology Division, The Ohio State University, The Heart Center, Nationwide Children's Hospital, 700 Children's Dr, Columbus, OH 43205. E-mail Ralf.Holzer@NationwideChildrens.org

Circ Cardiovasc Interv **is available at http://circinterventions.ahajournals.org** **DOI: 10.1161/CIRCINTERVENTIONS.110.961029**

Inclusion and Exclusion Criteria

All cases in which PA angioplasty and/or stent placement was performed in at least 1 proximal, lobar, or sublobar branch PA were included (no exclusions). Reports have suggested a difference in technical considerations and acute procedural results of balloon angioplasty when comparing proximal and distal lesions.[11] Therefore, procedures were separated into 3 groups: (1) proximal: Balloon angioplasty and/or stent placement performed only on proximal branch PAs, between the origin of either right or left PA, and the take-off of the first lobar branch; (2) lobar: balloon angioplasty and/or stent placement performed only on lobar and/or sublobar branch PAs, distal to the take-off of the first lobar branches; and (3) mixed: balloon angioplasty and/or stent placement performed on proximal and lobar/sublobar branch PAs.

Each case was considered to represent an independent opportunity for an adverse outcome and characterize the population of patients treated during the time period at the participating institutions. However, to facilitate analysis of reintervention, the data base administrator assigned each procedure a unique numeric patient identifier. Cases that had the same patient initials, hospital identifier, and date of birth were assigned the same numeric patient identifier.

Data Collected

Variables collected included demographic data (age, weight), clinical data (underlying diagnosis, previous catheter, and surgical procedures), case data (type of anesthesia, case time defined from sheath entry to sheath removal, fluoroscopy time, contrast amount, vascular access, interventions performed), hemodynamic and oxymetry data (mixed venous saturations, systemic arterial saturations, systolic right and systemic ventricle pressure, systemic end-diastolic pressure, main pulmonary artery pressure), as well as other details (inotropic support and use of extracorporeal membrane oxygenation). The impact of (predictor) variables on incidence of adverse events was evaluated.

Hemodynamic variables associated with vulnerability for AE were determined on the basis of on an empirical analysis of the full C3PO data set.[12] Briefly, univariate analysis identified factors associated with clinically important (levels 3, 4, and 5) adverse events and subsequently a multivariate logistic model based on this outcome was built in a forward stepwise manner. The final model with the best predictive performance for high-severity adverse events included systolic main PA pressure ≥45 mm Hg (2-ventricle) or mean PA pressure ≥17 mm Hg (single ventricle), systemic ventricular end-diastolic pressure ≥18 mm Hg, mixed venous saturations <60% (2-venricle) or mixed venous saturation <50% (single ventricle), and systemic saturations <95% (2-ventricle) or <78% (single ventricle). Hemodynamic vulnerability was defined as none, 1, or ≥2, based on the total number of hemodynamic vulnerability variables present.

All AE were captured, and each AE was assigned a severity category from 1 to 5 (none, minor, moderate, major, and catastrophic) and preventability designation (not preventable, possibly preventable, and preventable) as defined in the International Pediatric Congenital Cardiology Code nomenclature[13] (online-only Data Supplement Tables S1 and S2). All AE were independently reviewed (nonblinded) by 2 interventional cardiologists for proper and consistent application of seriousness and preventability categorization. Differences in the assignments of severity and preventability were resolved between reviewer and operator for each individual case (reviewer assessment taking precedence).

Completeness of case capture was confirmed by requiring institutions to cross-check a list of cases entered into the data base with institutional records. Cases that had been missed were added to the data base retrospectively. Participants were sent monthly exception reports to facilitate capture of any missing data. After the first 15 months of the study period, a random audit of 10% of cases was performed at each participating institution, documenting a 92% capture rate of high severity (level 3 to 5) AE.[10]

Statistical Analysis

Descriptive patient and case characteristics were provided for all cases and were stratified by case type (proximal, lobar, and mixed).

Table 1. Patient and Population Characteristics

Population Characteristics	Total (n=1315)	Proximal (n=789)	Lobar (n=226)	Mixed (n=300)
Age, y	3.5	3.2	5	2.7
	0–70	0–55.4	0–70.4	0–59.6
	[1, 10.8]	[0.8, 11]	[1.8, 12]	[1.2, 8.7]
Weight, kg	13.6	13.5	17.5	12.7
	1.8–151	1.8–151	2.4–143	1.8–106.8
	[8.2, 33.4]	[7.4, 35.5]	[9.6, 40]	[8.6, 24.9]
Diagnosis				
Single ventricle	291 (22)	255 (32)	15 (7)	21 (7)
2-Ventricle: Isolated defects	56 (4)	27 (3)	14 (6)	15 (5)
2-Ventricle: Complex defect	937 (71)	496 (63)	178 (79)	263 (88)
2-Ventricle: Other	31 (2)	11 (1)	19 (8)	1 (<1)
Genetic abnormality	246 (19)	127 (16)	58 (26)	61 (20)

For categorical variables, n (%) is provided; median, range, and interquartile range [in separate rows] are provided for continuous variables.

Multiple procedures performed in the same patient were presumed to be independent from each other. Median, range, and interquartile range were calculated for all continuous variables and frequency with percentages for categorical variables. Patient and case characteristics were compared across these 3 groups, using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Additional comparisons of 2 groups (eg, for cases with single-ventricle physiology versus 2-ventricle physiology) were performed using the Wilcoxon rank-sum test or the χ^2 test. The Spearman rank-correlation coefficient was used to evaluate the relationship between number of interventions and the case and fluoroscopy times.

Patient and procedural characteristics were assessed in univariate analysis for a relationship with any AE, any high-severity AE, and subsequent reintervention. For demographic, clinical, hemodynamic, and procedural variables, the χ^2 test was used for univariate comparisons. For institutional and operator variables, generalized estimating equations models were used to account for the correlation among patients from the same hospital (hospital volume) or having the same operator (operator experience, and operator volume).

Predictors that were statistically significant in univariate analysis ($P<0.1$) were included in the multivariate analysis. Generalized estimating equations models using forward selection were used for multivariate analysis; variables significant at the 0.05 level based on the likelihood ratio test were retained in the final models. Odds ratios (OR) and 95% confidence intervals were provided. With the exception of selecting factors for the multivariate model, all other tests were considered statistically significant if $P<0.05$. StatsDirect 2.7.8 as well as SAS 9.2 were used for statistical calculations.

Results

Between February 1, 2007, and December 31, 2009, 11 804 cardiac catheterization cases were entered into the C3PO registry. Of these 11 804 cases, 1315 (11%), performed in 969 patients, met the inclusion criteria.

PA rehabilitation was performed exclusively on proximal PAs in 789 cases (60%), exclusively on lobar locations in 226 cases (17%), and on mixed locations in 300 cases (23%). Additional interventions were performed in 440 cases (33%) (Table 1 and Table 2).

Population and Case Characteristics

The median age was 3.5 years (1 day to 70 years), and the median weight was 13.6 kg (1.8 to 151 kg) (Table 1 and

Table 2. Case Characteristics

Case Characteristics	Total (n=1315)	Proximal (n=789)	Lobar (n=226)	Mixed (n=300)	*P* Value
Type of case					0.002
Elective case	1115 (85)	647 (82)	199 (88)	269 (90)	
Nonelective or emergent	200 (15)	142 (18)	27 (12)	31 (10)	
Within 30 d of					
Previous catheter procedure	85 (6)	49 (6)	20 (9)	16 (5)	0.24
Previous surgical procedure	114 (9)	80 (10)	22 (10)	12 (4)	0.005
Case duration, min	141	128	161	160	<0.001
	5–566	5–566	56–370	64–441	
	[106, 187]	[99, 171]	[121, 201]	[128, 208]	
Fluoroscopy time, min	48	40	59	65	<0.001
	0–235	0–235	17–192	1–194	
	[32, 71]	[27, 59]	[40, 80]	[47, 91]	
Contrast dose, mL/kg	5.3	5.2	5.0	5.9	<0.001
	0–16.9	0–16.9	0.6–13.4	0.6–15.1	
	[3.7, 7.1]	[3.5, 6.9]	[3.3, 7.1]	[4.4, 7.7]	
Non-PA interventions	440 (33)	324 (41)	35 (15)	81 (27)	<0.001

For categorical variables, n (%) is provided: median, range, and interquartile range [in separate rows] are provided for continuous variables.

PA indicates pulmonary artery.

online-only Data Supplement Table S3). The underlying anatomy was single ventricle in 22%, complex 2-ventricle in 71%, and other anatomy in 7%. An underlying genetic abnormality was present in 19% of cases. The majority (85%) of cases were elective. Cases performed within 30 days of preceding cardiac surgery accounted for 9% of all cases. General anesthesia with a secured airway was used in 81% of cases. Two percent of cases were performed using a Hybrid approach.

Hemodynamic Data

In patients with a 2-ventricle circulation 10% had suprasystemic right ventricular pressures. Patients met hemodynamic vulnerability criteria for main PA pressure in 34%, systemic saturation in 33%, mixed venous saturations in 16%, and end-diastolic pressure in 4%. Two or more parameters of hemodynamic vulnerability were present in 24% of cases, whereas just 1 parameter was present in 33% of cases (online-only Data Supplement Table S4). When comparing the lobar and mixed groups with the proximal group, there was a higher incidence of cases with 1 (42% versus 41% versus 28%) or ≥2 (30% versus 30% versus 20%) parameters of hemodynamic vulnerability.

PA Interventions

PA rehabilitation was performed on proximal PAs in 60% of cases, lobar locations in 17%, and mixed locations in 23%. Cases that only involved the proximal branch PAs were more likely to undergo additional non-PA interventions (41% versus 22%, $P<0.001$). Lobar or mixed interventions were less common in patients with single-ventricle physiology when compared with those with 2-ventricle physiology (12% versus 48%, $P<0.001$).

More than 1 PA intervention was performed in 57% of cases, whereas ≥5 PA interventions were performed in 9% of cases, even though they accounted for <5% of all PA rehab procedures in 4 of the 8 institutions. Multiple PA interventions were less common in the proximal group when compared with the lobar and mixed group (35% versus 75% versus 100%, $P<0.001$). The percentage of patients with an underlying genetic syndrome was higher in cases in which multiple PA interventions were performed when compared with those cases that required only a single PA intervention (25% versus 17%, $P=0.014$).

The type of PA interventions performed is listed in Table 3. Balloon angioplasty with a maximum pressure <8 atm was performed in 26% of cases, balloon angioplasty with maximum pressure >8 atm in 43%, stent angioplasty in 24%, cutting balloon angioplasty in 17%, and stent implantation in 37% (premounted 17%, nonpremounted 20%). Stent implantation was significantly more common in the proximal group when compared with the lobar and mixed group (43% versus 23% versus 32%, $P<0.001$), whereas cutting balloon angioplasty was more frequently used in the lobar and mixed group when compared with the proximal group (38% versus 39% versus 2%, $P<0.001$).

Premounted stents accounted for 46% of all stent implantations, with their use being more common in younger patients (median age, 1.5 years versus 7.4 years for nonpremounted, $P<0.001$) and in nonelective/emergent cases or cases performed within 30-days of surgery when compared with other cases (37% versus 11%, $P<0.001$). The majority (51%) of premounted stents were implanted in proximal PAs, with 40% of those being implanted in patients >1 year of age.

The median case time was 141 minutes (5 to 566 minutes) and the median fluoroscopy time was 48 minutes (0 to 235

Table 3. Technical Procedural Characteristics

	Total (n=1315)	Proximal (n=789)	Lobar (n=226)	Mixed (n=300)	*P* Value
Type of intervention					
Balloon angioplasty, <8 atm	348 (26)	178 (23)	71 (31)	99 (33)	<0.001
Balloon angioplasty, ≥8 atm	565 (43)	225 (29)	139 (62)	201 (67)	<0.001
Cutting balloon angioplasty	221 (17)	19 (2)	86 (38)	116 (39)	<0.001
Premounted stent	224 (17)	114 (14)	41 (18)	69 (23)	0.003
Nonpremounted stent	261 (20)	221 (28)	11 (5)	29 (10)	<0.001
Covered stent	9 (1)	4 (1)	2 (1)	3 (1)	0.63
Self-expanding	1 (<1)	1 (<1)	0 (0)	0 (0)	0.72
PA interventions, n					<0.001
1	566 (43)	510 (65)	56 (25)	0 (0)	
2	370 (28)	240 (30)	62 (27)	68 (23)	
3	164 (12)	29 (4)	48 (21)	87 (29)	
4	93 (7)	9 (1)	28 (12)	56 (19)	
≥5	122 (9)	1 (<1)	32 (14)	89 (30)	
Interventions on both PAs	462 (35)	200 (25)	73 (32)	189 (63)	<0.001

Details are provided on type and number of interventions performed. For categorical variables, n (%) is provided. Type of intervention can add to >100% because a case can be presented in >1 category.
PA indicates pulmonary artery.

minutes). Hybrid procedures had associated cases times as low as 5 minutes, and 24% of hybrid procedures were performed without the use of fluoroscopy. There was a significant correlation between the number of PA interventions performed and the case time (r=0.29; 95% confidence interval [CI], 0.23 to 0.34; P<0.001), as well as the fluoroscopy time (r=0.38; 95% CI, 0.33 to 0.43; P<0.001). Cases with proximal PA interventions only with or without additional non-PA interventions had significantly shorter median case times than those in the lobar or mixed group (128 minutes versus 161 minutes versus 160 minutes, P<0.001) and fluoroscopy times (40 minutes versus 59 minutes versus 65 minutes, P<0.001). The median contrast load was 5.3 mL/kg, ranging from 0 to 16.9 mL/kg. In 6.5% of cases a total amount of contrast equal to or in excess of 10 mL/kg was administered.

Adverse Events

An AE occurred in 22% of cases, with high severity level 3 to 5 AE occurring in 10% of cases (online-only Data Supplement Table S5). Two patients (0.015%) died as a direct result of the procedure. Levels of severity of AE are listed in Table 4. Thirty-eight life-threatening level 4 to 5 AE (Table 4) occurred including vascular tears (n=8), stent malposition/embolization requiring surgical intervention (n=5), endotracheal bleeding or hemodynamically important reperfusion injury (n=4), asystole, heart block, or other hemodynamic instability related to catheter and/or wire manipulation requiring full resuscitation (n=6), and postprocedural upper airway obstruction (n=1). There were 8 level 4 to 5 AE that were unrelated to the PA rehabilitation procedure, and for 6 events the relationship to the type of intervention was unclear.

AE were less common in the proximal group when compared with the lobar or mixed group (20% versus 23% versus 26%, P<0.05). Types of adverse events are listed in Table 5. When comparing the proximal with the lobar and mixed groups, technical AE (23% versus 3% versus 9%, P=0.002) were more common, whereas vascular trauma (11% versus 29% versus 23%, P=0.001) and bleeding via the endotracheal tube or reperfusion injury (5% versus 21% versus 20%, P<0.001) were less common.

Table 4. AE by Level of Severity

	All AE				
AE by Severity	Total (n=324)	Proximal (n=174)	Lobar (n=61)	Mixed (n=89)	*P* Value
Level 1: None	30 (9)	18 (10)	3 (5)	9 (10)	0.61
Level 2: Minor	143 (44)	72 (41)	33 (54)	38 (43)	
Level 3: Moderate	107 (33)	59 (34)	18 (30)	30 (34)	
Level 4: Major	36 (11)	23 (13)	7 (11)	6 (7)	
Level 5: Death	2 (1)	1 (1)	0 (0)	1 (1)	
Unknown severity	6 (2)	1 (1)	0 (0)	5 (6)	

For categorical variables, n (%) is provided.
AE indicates adverse events.

Table 5. Types of AE

	All AE				
AE Details	Total (n=324)	Proximal (n=174)	Lobar (n=61)	Mixed (n=89)	*P* Value
Vascular/cardiac trauma	60 (19)	20 (11)	14 (23)	26 (29)	0.001
Confined tear	23 (7)	7 (4)	6 (10)	10 (11)	
Tear with flow obstruction	9 (3)	2 (1)	2 (3)	5 (6)	
Unconfined tear	9 (3)	0 (0)	5 (8)	4 (4)	
Aneurysm/pseudoaneurysm	5 (2)	2 (1)	0 (0)	3 (3)	
Heart perforation	1 (0)	1 (1)	0 (0)	0 (0)	
Hemothorax	2 (1)	2 (1)	0 (0)	0 (0)	
Other vessel trauma	11 (3)	6 (3)	1 (2)	4 (4)	
Technical AE	50 (15)	40 (23)	2 (3)	8 (9)	<0.001
Balloon rupture	17 (5)	12 (7)	1 (2)	4 (4)	
Stent malposition/embolization	21 (6)	18 (10)	0 (0)	3 (3)	
Other stent-related problem	12 (4)	10 (6)	1 (2)	1 (1)	
Arrhythmias	49 (15)	32 (18)	11 (18)	6 (7)	0.02
Atrial arrhythmia	9 (3)	5 (3)	0 (0)	4 (4)	
Heart block, resolved	37 (11)	23 (13)	10 (16)	4 (4)	
Ventricular arrhythmia	5 (2)	4 (2)	1 (2)	0 (0)	
Hemodynamic AE	45 (14)	24 (14)	10 (16)	11 (12)	0.77
Asystole/cardiac arrest	4 (1)	2 (1)	1 (2)	1 (1)	
Bradycardia, sinus	6 (2)	3 (2)	3 (5)	0 (0)	
Hypotension, no intervention	12 (4)	7 (4)	2 (3)	3 (3)	
Hypotension, inotropes or volume	15 (5)	8 (5)	1 (2)	6 (7)	
Hypoxia	3 (1)	2 (1)	1 (2)	0 (0)	
Nonspecific ST/T-wave changes	5 (2)	2 (1)	2 (3)	1 (1)	
Reperfusion injury/ETT bleed	40 (12)	9 (5)	12 (20)	19 (21)	<0.001
Vascular entry site AE	34 (10)	22 (13)	5 (8)	7 (8)	0.45
Local hematoma	12 (4)	8 (5)	1 (2)	3 (3)	
Pulse loss	6 (2)	3 (2)	2 (3)	1 (1)	
Rebleed	6 (2)	3 (2)	1 (2)	2 (2)	
Other problem	10 (3)	8 (5)	1 (2)	1 (1)	
Sedation/anesthesia/airway	12 (4)	5 (3)	3 (5)	4 (4)	0.57
Airway obstruction	5 (2)	2 (1)	0 (0)	3 (3)	
Respiratory acidosis	3 (1)	1 (1)	2 (3)	0 (0)	
Other	4 (1)	2 (1)	1 (2)	1 (1)	
Other	34 (10)	22 (13)	4 (7)	8 (9)	0.41
Allergic reaction	3 (1)	2 (1)	0 (0)	1 (1)	
Neurological problem	1 (<1)	1 (1)	0 (0)	0 (0)	
Renal insufficiency/failure	2 (1)	1 (1)	0 (0)	1 (1)	
Other	28 (9)	18 (10)	4 (7)	6 (7)	

ETT indicates endotracheal tube; AE, adverse events.

For categorical variables, n (%) is provided with the percentage being displayed as percentage of all AE seen in the procedural type category (total, proximal, lobar, or mixed).

There was no significant difference among the 3 subgroups with regard to the incidence of preventable or possibly preventable AE. AE were classified as not preventable in 50%, possibly preventable in 41%, and preventable in 9% (online-only Data Supplement Table S6). Preventable AE (n=29) were variable and are listed in Table 6. None of the arrhythmias were classified as a preventable AE. There was no difference in the severity of adverse events when comparing preventable with not/possibly preventable adverse events: The incidence of high-severity adverse events was 41% among preventable AE and 45% among not/possibly preventable adverse events ($P=0.632$).

Although the exact relationship with a procedural component could not always be clearly established for all AE, some

Table 6. Preventable AE Encountered

Vascular and cardiac injury	Anesthesia/sedation/airway-related AE
Wire perforation with hemothorax (n=1)	Self-extubation (n=1)
Dissection after hand-injection of contrast (n=2)	Airway obstruction (n=1)
Transient hemoptysis related to guide wire manipulation (n=1)	Anesthesia equipment failure (n=1)
Entering of pericardial space during transseptal puncture (n=1)	Brachial plexus injury (n=1)
Technical AE	Other AE
Stent migration/malposition (n=5)	Power injection through end-hole catheter (n=1)
Coil malposition/embolization (n=3)	Systemic air embolus with power injection (n=1)
AE associated with vascular entry	Use of wrong stent (n=1)
Sheath dislodgment with dissection (n=1)	Blood loss caused by stopcock left open (n=1)
Access site hematoma (n=1)	Other AE (n=1)
Inadvertent placement of sheath in carotid artery (n=1)	
Placement of sheath in femoral artery instead of vein (n=1)	

AE indicates adverse events.

AE such as coil malposition or entering of pericardial space during transseptal puncture were clearly related to additional interventions performed in the same setting.

Predictors of AE

There were multiple patient and procedural characteristics associated with an occurrence of AE in univariate analysis, for both, any, and level 3 to 5 AE (Table 7 and online-only Data Supplement Table S7). However, in multivariate analysis, the independent risk factors for high-severity level 3 to 5 AE were ≥2 parameters of hemodynamic vulnerability (OR, 1.65; CI, 1.07 to 2.54), age <1 month (OR, 2.52; CI, 1 to 6.32), use of cutting balloon (OR, 1.64; CI, 1.25 to 2.15), as well as operator experience <10 years (OR, 1.61; CI, 1.02 to 2.54). Even though the incidence of high-severity level 3 to 5 AE was higher for operators with <10 years of experience, there was no notable difference in the type of AE seen. Furthermore, the percentage of preventable or possibly preventable AE was not significantly higher when compared with more experienced operators (5.2% versus 4.8%, $P=0.572$).

For any AE, independent predictors by multivariate analysis were ≥2 parameters of hemodynamic vulnerability (OR, 1.66; CI, 1.24 to 2.22), use of cutting balloon (OR, 1.94; CI, 1.26 to 2.98), age <1 month (OR, 2.59; CI, 1.37 to 4.87), as well as non-PA interventions (OR, 1.48; CI, 1.13 to 1.93). In contrast to level 3 to 5 AE, operator experience of <10 years was not identified as an independent risk factor for any AE.

Institutional and operator case load as well as number of PA rehabilitation procedures did not have an association with the occurrence of level 3 to 5 or any AE. Table 8 lists the institutional case loads and frequency of PA rehabilitation procedures for all 8 participating centers as well as incidence of AE per center.

Reinterventions

The median follow-up over the study period was 16 months (1 day to 35 months). Of 969 patients, 215 (22%) underwent 346 reinterventions during the study period. Only 1 reintervention was performed in 141 (15%) patients, whereas 74 (8%) patients had >1 reintervention during the study period. For the 215 patients with at least 1 reintervention, median time between the first and second procedure was 181 days (1 to 896 days). Reinterventions were less common in the proximal group when compared with the lobar or mixed group (15% versus 39% versus 39%, $P<0.001$).

Independent factors associated with reintervention included age <18 years, lobar or mixed interventions, nonelective or emergent procedures, and institutional case volume >500 procedures per year (for OR and 95% CI, see online-only Data Supplement Table S8).

Discussion

In this cohort of 1315 transcatheter PA interventional cases, AE occurred in 22% of all cases, and high-severity (level 3 to 5) AE occurred in 10% of cases, notably higher than what has been previously reported; however, mortality was much less common.[14] The majority (74%) of level 3 to 5 AE were level 3, which by definition are not associated with permanent disability. This study is the first to highlight the importance of operator experience as a potential risk factor for high severity level 3 to 5 AE. Furthermore, this study has documented important differences between proximal lesions as well as lobar/mixed lesions, relating to interventional technique as well as adverse events.

Procedural Technique and AE

This study has provided important data to aid in procedural planning as well as preprocedure counseling of patients who require PA rehabilitation. All forms of balloon angioplasty and the use of premounted stents were more common in the lobar and mixed groups, whereas nonpremounted stents were used more commonly in the proximal group.

Even though the majority of premounted stents cannot be expanded to adult size, they were used in close to 50% of all stent implantation. Although redilation of large-diameter stents is known to be feasible and highly successful even after 10 years after implantation,[5] this is not he case for the common premounted small and medium diameter stents, in which vessel growth can easily exceed the diameter that can be accommodated with these stents. Even though surgical stent removal or plasty is feasible in many patients,[15] creating a future area of stenosis resulting from diameter limitations of the implanted stent should be avoided. However, there are some valid reasons for using small and medium diameter stents in a proximal PA position, which may explain the high usage in this patient population. These include limitations of the vessel size (small diameters, short length), maximum stent diameter not exceeding the projected adult-size vessel, as well as hemodynamic instability, with inability to tolerate the use of large sheaths and stiff wires. In these patients,

Table 7. Predictors of Any Level 3 to 5 AE

	High-Severity Level 3 to 5 AE		Univariate	Multivariable Analysis	
Predictor	N	Any 3 to 5 AE (%)	*P* Value	*P* Value	OR (95% CI)
Demographic/clinical predictors					
Age			0.01		
<1 mo	34	8 (24)		0.05	2.52 (1.00, 6.32)
1 < 12 mo	285	40 (14)		0.68	1.11 (0.68, 1.82)
1 < 10 y	644	56 (9)		0.41	0.77 (0.42, 1.43)
10 < 18 y	202	17 (8)		0.59	0.83 (0.42, 1.63)
≥18 y	150	15 (10)		. . .	1.00
Genetic abnormality present	246	24 (10)	0.73		
Diagnosis			0.55		
Single ventricle	291	35 (12)			
Complex 2-ventricle	937	93 (10)			
Other	87	8 (9)			
Hemodynamic predictors					
Hemodynamic vulnerability			0.009		
0	559	44 (8)		. . .	1.00
1	438	46 (11)		0.31	1.18 (0.86, 1.61)
2+	318	46 (14)		0.02	1.65 (1.07, 2.54)
Procedural predictors					
Location of PA rehab			0.69		
Proximal	789	78 (10)			
Lobar	226	23 (10)			
Mixed	300	35 (12)			
Nonelective or emergent procedures	200	34 (17)	0.001		
Airway management			0.14		
Intubated before start/transfer	1069	117 (11)			
Spontaneous respiration	245	19 (8)			
Previous cath procedures			0.63		
None documented	206	24 (12)			
1	248	22 (9)			
2	229	21 (9)			
3	178	23 (13)			
≥4	410	42 (10)			
Days since last surgery or cath <30	147	22 (15)	0.06		
Bilateral interventions	462	48 (10)	0.97		
Any non-PA intervention	440	49 (11)	0.50		
Risk category for non-PA intervention*			0.30		
PA intervention only	875	87 (10)			
Unable to be assigned	11	1 (9)			
1	27	5 (19)			
2	235	26 (11)			
3	139	12 (9)			
4	28	5 (18)			
PA interventions, n			0.08		
Single	566	53 (9)			
2	370	32 (9)			
3	164	22 (13)			
4	93	9 (10)			
≥5	122	20 (16)			

(*Continued*)

Table 7. Continued

Predictor	High-Severity Level 3 to 5 AE		Univariate	Multivariable Analysis	
	N	Any 3 to 5 AE (%)	*P* Value	*P* Value	OR (95% CI)
Procedural technique					
Balloon angioplasty, <8 atm	348	32 (9)	0.41		
Balloon angioplasty, >8 atm	565	59 (10)	0.92		
Cutting balloon angioplasty	221	32 (14)	0.03	<0.001	1.64 (1.25, 2.15)
Premounted stent	224	32 (14)	0.03		
Nonpremounted stent	261	31 (12)	0.36		
Institutional/operator predictors					
≥500 cases/center/y	862	83 (10)	0.22		
≥40 PA rehab/center/y	1135	121 (11)	0.28		
≥200 cases/operator/y	899	92 (10)	0.85		
≥20 PA rehab/operator/y	1007	107 (11)	0.52		
Operator experience (since fellowship)					
<10 y	575	77 (13)	0.008	0.04	1.61 (1.02, 2.54)
≥10 y	704	56 (8)		. . .	1.00

Predictors of any level 3 to 5 AE in patients undergoing balloon angioplasty and/or stent placement of branch PAs. PA indicates pulmonary artery; AE, adverse events.

*Risk group for non-PA intervention was defined according to Bergersen et al.[16]

implanted small-diameter stents can potentially be fractured, as shown recently by Maglione et al,[17] through the use of ultra–high-pressure balloons. Hybrid stent delivery, used in 2% of all cases, has been shown to be a suitable alternative in selected patients[18] and may be particularly helpful when large-diameter stents must be implanted in small and/or hemodynamically unstable patients.

Balloon angioplasty alone remains a very important treatment modality, particularly for small lobar and sublobar branches. However, recurrence rate after standard balloon angioplasty in excess of 10% within 1 year of the procedure have been well documented.[11] An alternative, especially for resistant lesions, is the use of cutting balloon angioplasty, which has been shown to achieve significant improvements in vessel diameters, with restenosis rates similar to conventional angioplasty.[19] Although the use of cutting balloons was found to be an independent risk factor for any AE as well as high severity level 3 to 5 AE, this may be an indicator of the severity of the underlying lesion, rather than a side effect of the procedural technique; however, parameters of severity and complexity of a lesion, such as morphology, tightness, or sublobar location, were not collected in this registry.

Cutting balloon angioplasty was used more frequently in the lobar and mixed group, where important AE, such as vascular injury as well as reperfusion injury or bleeding via the endotracheal tube, were more common as opposed to just proximal lesions. In contrast to isolated proximal lesions, patients with lobar lesions often have generalized PA disease with persistent main PA hypertension even after angioplasty and/or stent placement, which can result in increased distal PA pressures of the rehabilitated segment, which may explain the higher incidence of reperfusion injury. Arnold et al[20] documented acute changes in distal PA pressures >150% and a mean distal PA pressure of >20 mm Hg after intervention as risk factors for reperfusion injury. Treating as many branch PA lesions as possible may have the greatest potential to effectively relief the main PA pressures, thereby reducing the risk of distal PA hypertension and reperfusion injury. Although the incidence of bleeding via the endotracheal tube was as high as 12%, it is unclear whether all these represent

Table 8. AE Observed at Different Centers

Cases per Center (n)	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8
All cath cases, ~per year	583	1330	418	420	360	477	652	290
PA rehab, C3PO total	129	659	68	139	134	93	74	19
PA rehab, ~per year	44 (8)	226 (17)	23 (6)	48 (11)	46 (13)	32 (7)	40 (6)	38 (13)
Cases with any AE	26 (20)	156 (24)	4 (6)	36 (26)	35 (26)	22 (24)	5 (7)	3 (16)
Cases with level 3 to 5 AE	11 (9)	69 (10)	3 (4)	18 (13)	20 (15)	9 (10)	3 (4)	3 (16)

Center 7 and center 8 only joined the registry late and did not participate throughout. The percentage displayed for AE refers to the percentage of all PA rehab cases in the registry, whereas the percentage provided for PA rehab procedures per year refers to the percentage of all catheterization procedures performed on average per year by the respective institution.

AE indicates adverse events; CP30, Congenital Cardiac Catheterization Project on Outcomes; PA, pulmonary artery.

typical reperfusion injury, or whether some of these instances may have been related to using small stiff 0.018 in wires, which can readily perforate the wall of small pulmonary vasculature.

In contrast to reperfusion injury, technical complications were more common in proximal lesions. Achieving a stable balloon position can be more challenging and operators are therefore more likely to encounter complications such as stent migration or stent embolization. However, the data do not reflect the incidence of jailing of adjacent vascular branches, which may be more common for lobar lesions, and which was not captured in the C3PO registry.

Although the operator can influence the procedural technique that is being used, other risk factors are less modifiable. This study has identified multiple indicators of hemodynamic vulnerability, and low patient age as independent risk factors for all AE as well as for the more severe level 3 to 5 AE. Although important for preprocedural counseling, frequently there is very little the operator can do to mitigate these risks because catheterization is often the only feasible remaining treatment modality to eliminate important (residual) anatomic problems in these patients.

This study has documented a significantly higher incidence of high level AE in operators with <10 years of experience. The fact that this study did not demonstrate an increased percentage of preventable AE in these operators, suggests that the higher incidence of AE is more likely secondary to subtle differences in operator technique and judgment rather than gross mistakes or errors. This highlights the importance of young interventionalists to be mentored by an experienced operator during the early stages of their career as an independent operator. Interestingly, operator experience did not appear to be an independent risk factor when looking at all AE. Guidance, therefore, is most important during "crucial" elements of a procedure that are more likely to have associated high severity level 3 to 5 AE if suboptimal technique is used. Examples would include stent, balloon and wire choice (and position), which affect important possible higher level AE such as vascular/cardiac trauma, stent migration, and reperfusion injury/bleeding via the endotracheal tube.

Reinterventions

Early reinterventions occurred in 22% of patients. However, reinterventions are often planned and part of a long-term treatment strategy that is aimed at ultimately rendering the pulmonary vasculature suitable for a full biventricular repair with ventricular septal defect closure. Reinterventions therefore represent not necessarily a procedural failure but rather a conscious therapeutic strategy to improve pulmonary vascular growth. Furthermore, a variable referral base as well as different interventional treatment strategies further account for differences in early reinterventions between institutions.

Limitations

The study is limited by the lack of procedural data relating to the efficacy of the balloon angioplasty and/or stent placement that was performed. Although AE are important, the incidence would need to be judged on the basis of whether the transcatheter therapy achieved its intended purpose. Furthermore, the collected data did not allow attributing each AE with the individual intervention (eg, stent, balloon angioplasty, or cutting balloon) and/or location (proximal, lobar, or sublobar). Furthermore, indicators of morphological severity and complexity of a lesion were not captured because AE and performed interventions were captured independent from each other. In addition, sublobar location was not captured but instead included within the lobar group. Some important clinical data are missing, such as classification of a branch PA stenosis as primary or postsurgical, additional anatomic details (eg, unifocalized collateral vessels versus native PA branches), or details of previous surgical procedures. Although an effort has been made to report all AE, it is likely that some AE, especially those of lesser significance (level 1 to 2) may have not been captured completely. Furthermore, although acute AE are well captured, the registry does not provide data on medium or long-term AE, such as aneurysms and stent fracture. The data set did not allow at this time for risk stratification analysis.

Conclusions

Transcatheter PA interventional therapy has a 22% risk of associated procedure-related AE, with higher-severity events occurring in 10%. Presence of >2 indicators of hemodynamic vulnerability, low weight, use of cutting balloons, as well as operator experience of <10 years were significant independent risk factors for high severity level 3 to 5 procedure-related AE. Whenever possible, patients must be hemodynamically stabilized before considering PA rehabilitation. Young operators with little experience in PA rehabilitation should be familiar with procedural risks and ideally have close mentoring to limit the incidence of procedure-related AE. Small patients with multilevel PA disease involving lobar or mixed locations have a higher incidence of reinterventions, probably reflecting the therapeutic treatment strategy, which includes frequent planned transcatheter interventions. Operators must be aware of all typical risks of these procedures when counseling patients and families.

Acknowledgments

We thank the study coordinators and personnel who made this project feasible: Gary Piercey, Anniece Woods-Brown, Terri Mclees-Palinkas, Cyndi Murphy, and Joanne Chisolm.

Sources of Funding

Dr Bergersen is principal investigator for the C3PO project, which received grant support from the American Heart Association Physicians Roundtable Award (AHA-PRA). A web-based application for data entry was developed in 2006 with funding support from the Children's Heart Foundation (Chicago, IL). The application was deployed on a Microsoft Internet Information Server (IIS) obtained with funding support from the American Heart Association.

Disclosures

Dr Bergersen and Dr Lock are also coinvestigators for a multicenter study evaluating the safety and efficacy of cutting balloon to treat resistant PA stenosis; Boston Scientific Corporation provided monetary support for this study and devices. The following authors participate in the COAST trial, evaluating bare metal and covered stents for the treatment of coarctation: Drs Bergersen, Lock, Cheatham, and Holzer. Dr Cheatham has a grant from AGA Medical Corporation to support the development of new devices for congen-

ital heart disease. Biomedical companies have consultant or advisory board relationships with the Dr Cheatham: TOSHIBA Medical Systems Corporation, AGA Medical Corporation, W.L. Gore & Associate, Inc, and Medtronic, Inc.

References

1. Bergersen L, Marshall A, Gauvreau K, Beekman R, Hirsch R, Foerster S, Balzer D, Vincent J, Hellenbrand W, Holzer R, Cheatham J, Moore J, Lock J, Jenkins K. Adverse event rates in congenital cardiac catheterization: a multi-center experience. *Catheter Cardiovasc Interv*. 2010;75:389–400.
2. Shaffer KM, Mullins CE, Grifka RG, O'Laughlin MP, McMahon W, Ing FF, Nihill MR. Intravascular stents in congenital heart disease: short- and long-term results from a large single-center experience. *J Am Coll Cardiol*. 1998;31:661–667.
3. McMahon CJ, El Said HG, Vincent JA, Grifka RG, Nihill MR, Ing FF, Fraley JK, Mullins CE. Refinements in the implantation of pulmonary arterial stents: impact on morbidity and mortality of the procedure over the last two decades. *Cardiol Young*. 2002;12:445–452.
4. McElhinney DB, Bergersen L, Marshall AC. In situ fracture of stents implanted for relief of pulmonary arterial stenosis in patients with congenitally malformed hearts. *Cardiol Young*. 2008;18:405–414.
5. McMahon CJ, El-Said HG, Grifka RG, Fraley JK, Nihill MR, Mullins CE. Redilation of endovascular stents in congenital heart disease: factors implicated in the development of restenosis and neointimal proliferation. *J Am Coll Cardiol*. 2001;38:521–526.
6. Kretschmar O, Sglimbea A, Pretre R, Knirsch W. Pulmonary artery stent implantation in children with single ventricle malformation before and after completion of partial and total cavopulmonary connections. *J Interv Cardiol*. 2009;22:285–290.
7. O'Laughlin MP, Slack MC, Grifka RG, Perry SB, Lock JE, Mullins CE. Implantation and intermediate-term follow-up of stents in congenital heart disease. *Circulation*. 1993;88:605–614.
8. Rothman A, Perry SB, Keane JF, Lock JE. Early results and follow-up of balloon angioplasty for branch pulmonary artery stenoses. *J Am Coll Cardiol*. 1990;15:1109–1117.
9. Baker CM, McGowan FX Jr, Keane JF, Lock JE. Pulmonary artery trauma due to balloon dilation: recognition, avoidance and management. *J Am Coll Cardiol*. 2000;36:1684–1690.
10. Gentles TL, Lock JE, Perry SB. High pressure balloon angioplasty for branch pulmonary artery stenosis: early experience. *J Am Coll Cardiol*. 1993;22:867–872.
11. Bergersen L, Gauvreau K, Lock JE, Jenkins KJ. Recent results of pulmonary arterial angioplasty: the differences between proximal and distal lesions. *Cardiol Young*. 2005;15:597–604.
12. Bergerson L, Gauvreau K, Marshall A, Kreutzer J, Beekman RH, Hirsch R, Foerster S, Balzer D, Vincent J, Hellenbrand WE, Holzer RJ, Cheatham JP, Moore JD, Burch GE, Armsby L, Lock JE, Jenkins KJ. Catheterization for Congenital Heart Disease Adjustment for Risk Method (CHARM). *J Am Coll Cardiol*. 2011;57:E473. Abstract.
13. Franklin RC, Jacobs JP, Tchervenkov CI, Beland MJ. Bidirectional crossmap of the short lists of the European Paediatric Cardiac Code and the International Congenital Heart Surgery Nomenclature And Database Project. *Cardiol Young*. 2002;12:431–435.
14. Kan JS, Marvin WJ Jr, Bass JL, Muster AJ, Murphy J. Balloon angioplasty–branch pulmonary artery stenosis: results from the valvuloplasty and angioplasty of congenital anomalies registry. *Am J Cardiol*. 1990; 65:798–801.
15. Stanfill R, Nykanen DG, Osorio S, Whalen R, Burke RP, Zahn EM. Stent implantation is effective treatment of vascular stenosis in young infants with congenital heart disease: acute implantation and long-term follow-up results. *Catheter Cardiovasc Interv*. 2008;71:831–841.
16. Arnold LW, Keane JF, Kan JS, Fellows KE, Lock JE. Transient unilateral pulmonary edema after successful balloon dilation of peripheral pulmonary artery stenosis. *Am J Cardiol*. 1988;62:327–330.
17. Bergersen LT, Gauvreau K, Marshall A, Kreutzer J, Beekman R, Hirsch R, Foerster S, Balzer D, Vincent J, Hellenbrand W, Holzer R, Cheatham JP, Moore J, Lock J, Jenkins K. Procedure type risk groups for pediatric and congenital cardiac catheterization. *Circ Cardiovasc Interv*. 2011;4: 188–194.
18. Maglione J, Bergersen L, Lock JE, McElhinney DB. Ultra-high-pressure balloon angioplasty for treatment of resistant stenoses within or adjacent to previously implanted pulmonary arterial stents. *Circ Cardiovasc Interv*. 2009;2:52–58.
19. Holzer RJ, Chisolm JL, Hill SL, Olshove V, Phillips A, Cheatham JP, Galantowicz M. "Hybrid" stent delivery in the pulmonary circulation. *J Invasive Cardiol*. 2008;20:592–598.
20. Bergersen L, Jenkins KJ, Gauvreau K, Lock JE. Follow-up results of cutting balloon angioplasty used to relieve stenoses in small pulmonary arteries. *Cardiol Young*. 2005;15:605–610.

CLINICAL PERSPECTIVE

This prospective study analyzed basic procedural data and adverse events of 1315 transcatheter pulmonary artery interventional cases. Adverse events occurred in 22% of all cases, and more severe (level 3 to 5) adverse events occurred in 10% of cases, notably higher than what has been previously reported. Presence of >2 indicators of hemodynamic vulnerability, low weight, use of cutting balloons, as well as operator experience of <10 years were significant independent risk factors for level 3 to 5 procedure-related adverse events. This is very important data because it provides operators for the first time solid data on type and frequency of procedure-related adverse events, which is crucial when consenting patients and families for these procedures. Furthermore, this study now allows a better understanding of risk factors for serious adverse events, which allows a better risk stratification and may reduce the incidence of major procedure-related adverse events.