Risk Factors for Major Early Adverse Events Related to Cardiac Catheterization in Children and Young Adults With Pulmonary Hypertension: An Analysis of Data From the IMPACT (Improving Adult and Congenital Treatment) Registry

Michael L. O'Byrne, MD, MSCE; Kevin F. Kennedy, MS; Joshua P. Kanter, MD; John T. Berger, MD; Andrew C. Glatz, MD, MSCE

Background—Cardiac catheterization is the gold standard for assessment and follow-up of patients with pulmonary hypertension (PH). To date, there are limited data about the factors that influence the risk of catastrophic adverse events after catheterization in this population.

Methods and Results—A retrospective multicenter cohort study was performed to measure risk of catastrophic adverse outcomes after catheterization in children and young adults with PH and identify risk factors for these outcomes. All catheterizations in children and young adults, aged 0 to 21 years, with PH at hospitals submitting data to the IMPACT (Improving Adult and Congenital Treatment) registry between January 1, 2011, and December 31, 2015, were studied. Using mixed-effects multivariable regression, we assessed the association between prespecified subject-, procedure-, and center-level covariates and the risk of death, cardiac arrest, or mechanical circulatory support during or after cardiac catheterization. A total of 8111 procedures performed in 7729 subjects at 77 centers were studied. The observed risk of the composite outcome was 1.4%, and the risk of death before discharge was 5.2%. Catheterization in prematurely born neonates and nonpremature infants was associated with increased risk of catastrophic adverse event, as was precatheterization treatment with inotropes and lower systemic arterial saturation. Secondary analyses demonstrated the following: (1) increasing volumes of catheterization in patients with PH were associated with reduced risk of composite outcome (odds ratio, 0.8 per 10 procedures; $P=0.002$) and (2) increasing pulmonary vascular resistance and pulmonary artery pressures were associated with increased risk ($P<0.0001$ for both).

Conclusions—Young patients with PH are a high-risk population for diagnostic and interventional cardiac catheterization. Hospital experience with PH is associated with reduced risk, independent of total catheterization case volume. (*J Am Heart Assoc*. 2018;7:e008142. DOI: 10.1161/JAHA.117.008142.)

Key Words: catheterization • outcomes research • pediatric • pulmonary hypertension

Pulmonary hypertension (PH) affects 2.1 to 3.7 children per million.[1–3] Despite strides in pharmacotherapy, it remains a condition with high mortality and morbidity. Right-sided heart catheterization remains the gold standard tool for diagnosis, classification, risk stratification, and longitudinal follow-up of these patients.[4] Right-sided heart catheterization is technically straightforward and ranked in the lowest risk stratum of procedural risk hierarchies.[5–7] However, patients with PH may be less stable than other children during induction of anesthesia, the procedure itself, and during recovery from anesthesia, with a resultant increase in the risk of catheterization-associated catastrophic adverse outcomes.

Elevated pulmonary artery (PA) pressure or indexed pulmonary vascular resistance (PVRI) are both components

<div style="border: 2px solid red;">

Clinical Perspective

What Is New?

- This study is the first cohort study of children and adolescents with pulmonary hypertension undergoing cardiac catheterization with a representative national sample of real-world practice, evaluating both the risk of catastrophic adverse outcome and factors influencing them.

What Are the Clinical Implications?

- The study provides a new accurate estimate of the risk of catheterization in this population, which is important for preprocedural evaluation of risk and benefit.
- This study also demonstrates a significant association between larger pulmonary hypertension case volume and lower risk of catastrophic adverse event, which should motivate research into whether the benefits seen at large centers are attributable to transmissible best practices or are intrinsic results of scale.

</div>

of all 3 published risk adjustment/risk prediction scores.[5,6,8] However, there is controversy about the magnitude of risk associated with heart-sided catheterization in patients with PH.[9] The risks of a catastrophic outcome with a catheterization vary widely, from 0% to 5.3%, depending on whether they are derived from single-center case series,[10–13] PH-specific clinical registries,[14,15] multicenter registries of cardiac catheterization,[16] or administrative databases.[17,18]

Measurement of risk is challenging because of the broad spectrum of disease severity, range of comorbid conditions, and relatively small individual hospital volumes. Attempts have been made to overcome these challenges with clinical registries[14,15] and with administrative databases.[17,18] Disease-specific registries, like the Tracking Outcomes in Pediatric Pulmonary Hypertension registry, can record clinically detailed information about a cohort of subjects. Expense and logistical complexity, however, limit their size and the scope of analyses possible. In addition, requirements for patient consent to participate introduce the possibility of recruitment bias. In contrast, administrative databases, such as the Pediatric Health Information System (PHIS), contain data on all patients treated at member hospitals. This allows for the expedient collection of information about the entire population at risk at many hospitals. These same studies are limited by clinical data that are not included in administrative databases (eg, hemodynamic data and detailed information about cardiac diagnoses and specific interventions). We sought to overcome these limitations by using data from the IMPACT (Improving Adult and Congenital Treatment) registry, a multicenter clinical registry of catheterizations in patients performed at both primary pediatric and general

hospitals in the United States. The IMPACT registry includes detailed clinical, hemodynamic, and procedural data on all catheterization procedures at contributing hospitals, providing a representative study sample of patients with PH undergoing catheterization. We performed a retrospective cohort study using data from the IMPACT registry to more accurately measure the risk of catastrophic adverse event during or after catheterization in this population and to identify risk factors for major adverse events. We also performed secondary analyses to assess whether (1) severity of PH (measured by PA pressure, PVRI, or cardiac index) and (2) procedural volume (PH-specific catheterization and total catheterization volume) influenced risk of catastrophic adverse events.

Methods

Data Source

The IMPACT registry is a clinical registry funded by the American College of Cardiology Foundation and managed by the National Cardiovascular Data Registry, with data from 88 pediatric and general hospitals performing cardiac catheterizations in children and adults with congenital heart disease at the time of this analysis. Participating centers collect information on all patients undergoing cardiac catheterization, including patient demographics, medical/surgical history, procedural information, and adverse events through hospital discharge. Data are recorded using standardized data elements and definitions. The database is subject to rigorous quality assurance standards.[19] Auditing procedures are still being developed.[19–21] The current study used data from IMPACT v1.0.1. Analysis was performed on deidentified data and, as such, does not represent human subjects research in accordance with the Common Rule (45 CFR 46.102[f]). Data, analytic methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure, because this is not consistent with the data-use agreement between study staff and the American College of Cardiology Foundation and the National Cardiovascular Data Registry.

Study Population and Study Procedures

The study population was identified by direct query of the IMPACT registry by analysts at the Mid America Heart Institute. It included subjects from birth until 21 years of age who underwent procedures recorded in the IMPACT registry between January 1, 2011, and December 31, 2015. The subjects had PH identified by IMPACT registry code (1400 for primary PH, 1385 for pulmonary vascular obstructive disease, and 1390 for pulmonary vascular obstructive disease [Eisenmenger]) or met the hemodynamic definition of PH from

2015 American Heart Association/American Thoracic Society Pediatric Guidelines[4] (ie, mean PA pressure, ≥25 mm Hg). Patients with elevated PA pressure were excluded if they had a ratio of pulmonary/systemic blood flow >1.5:1 and PVRI <4 WU/m^2, because their PA pressures reflected appropriate hemodynamics in the face of a significant left-to-right shunt rather than pulmonary vascular disease. To improve the sensitivity of our cohort ascertainment, we also included subjects whose PA pressure was missing and whose PVRI was ≥4 WU/m^2. Patients were excluded if they were undergoing PA balloon or stent angioplasty, to avoid contamination of the study sample with patients based on elevated main PA pressure that was the result of fixed anatomic stenosis. Similarly, patients undergoing isolated balloon valvuloplasty of either the pulmonary or aortic valves were also excluded. Procedures from centers submitting data for <6 months, procedures from centers performing <10 total PH catheterizations were excluded, extracorporeal membrane oxygenation (ECMO) or left ventricular assist device were in use before the case. Finally, cases in patients with single-ventricle heart disease were excluded.

Data collected included demographics, medical history (including preprocedure risk factors), hemodynamic data, and details of the procedure (specific interventions, anesthesia at start of the case, device used, and presence of a trainee). Outcomes of interest were mortality and major adverse events (cardiac arrest, new arrhythmia, new heart valve regurgitation, tamponade, air embolus, initiation of dialysis, embolic stroke, new ECMO, new ventricular assist device, unplanned cardiac, vascular, or other surgery, vascular complication requiring treatment, and repeated catheterization, all before discharge). Death in the IMPACT registry is coded as death before discharge. For death, the date of death is recorded. For other adverse outcomes, any event before discharge within 30 days is recorded.

Cause of PH was divided between the following: (1) idiopathic PH (IPAH), (2) PH associated with congenital heart disease, (3) PH with cardiomyopathy, (4) PH after orthotopic heart transplant, and (5) pulmonary vein stenosis and PH. Diagnoses were based on IMPACT codes recorded in the registry. Preprocedure medications are recorded in the IMPACT registry by 1 of 8 predefined drug classes (diuretics, antiarrhythmics, antihypertensives, antiplatelet agents, anticoagulants, β blockers, vasodilators, and inotropes). There is significant class overlap, because pulmonary vasodilators (inhaled NO, phosphodiesterase-5 inhibitors, prostacyclin analogues, calcium channel blockers, and endothelin receptor antagonists) can fall into several of these groups or may not be recorded at all. No field in the registry records the specific medications received; thus, there are no means of identifying specific medications or numbers of medications within a class.

Statistical Analysis

Standard descriptive statistics were calculated. Continuous variables were expressed as mean±SD or median (range and interquartile range [IQR]). Categorical variables were described as proportions and counts. Multiple catheterization procedures were performed on individual subjects during the study period. All eligible procedures were included, and all statistics are reported per procedure, except where noted.

The primary outcome was a composite outcome (catastrophic adverse outcome) composed of death on the day of catheterization or the day after catheterization and cardiac arrest or initiation of ECMO. Because it is not possible to assess the attributability of these events to the catheterization retrospectively in a multicenter registry, we restricted the time horizon for adverse events to improve attributability, as previous described.[17,18] ECMO and cardiac arrest in the IMPACT registry data dictionary measure ECMO or cardiac arrest within 30 days. Unlike death, there is no date attached to these outcomes in the registry. We studied the time distribution of these events to determine the time course of events after these events. For patients with cardiac arrest, >50% died or were discharged within 10 days of catheterization, suggesting a temporal association between the event and the catheterization. A similar analysis is less productive in the case of ECMO, which prolongs life, so it was not performed.

The goal of the primary analysis was to generate an estimate of the risk of catastrophic adverse event with appropriate adjustment for patient- and procedure-level factors. As such, no primary exposure was defined before analysis. All covariates were specified before analysis on the basis of previous studies and clinical suspicion: age group (with interaction for prematurity), cause of PH, genetic syndrome, cardiac operation in past 30 days, mechanical ventilation, renal insufficiency, precatheterization inotropes, precatheterization vasodilators, and interventional procedure performed during the procedure. The IMPACT registry has a validated procedural risk-adjustment model,[5] which includes procedure-risk categories. These were not used because the IMPACT procedure-risk categories combine patient age and specific procedure, which makes evaluation of their relative contribution impossible in subsequent analysis. Instead, the performance of a transcatheter intervention was recorded. No additional forward or backward selection was used to refine the model. Hierarchical logistic regression was used to analyze outcomes, with a random intercept for center included to account for clustering by hospital.

Analyses of risk factors for the secondary outcomes were performed similarly. Two additional prespecified analyses were performed, adding factors to our initial model: (1) assessing whether the addition of mean PA pressure,

PVRI, or cardiac index influenced risk of the primary outcome; and (2) center annual catheterization procedural volume and center annual PH catheterization volume. For the latter, a model was calculated including PVRI to provide the best case-mix adjustment; another model was calculated without PVRI. Hemodynamic parameters indicative of right ventricular diastolic and systolic dysfunction (eg, right atrial mean pressure or right ventricular end-diastolic pressure) are not recorded in the current iteration of the IMPACT registry, and so could not be used in these analyses. To evaluate whether assumptions about covariance in the chosen modeling strategy biased results, generalized estimating equation models for the primary risk model were calculated, with no significant differences in the point estimates and confidence intervals (CIs) relative to the mixed-effects model (Table S1).

A potential source of bias is inclusion of multiple catheterization procedures per individual patient. Patients undergo multiple catheterizations in some cases because of concern for severe disease, while at the same time having undergone multiple catheterizations is suggestive that the patient has not experienced a catastrophic adverse outcome with previous catheterizations. To assess whether inclusion of multiple catheterizations introduced significant bias, a sensitivity analysis was performed that restricted analysis to the first catheterization performed in each subject. As for the

primary model, an analogous generalized estimating equation model was calculated for first catheterizations (data not shown).

Missing data were rare (<1% of cases). Therefore, case elimination/restriction was used, with analysis restricted to cases with complete data. No imputation was applied.

A threshold for statistical significance was set at $P<0.05$. All data analysis was performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

Study Population

Between January 1, 2011, and December 31, 2015, 14 636 procedures meeting diagnostic criteria for PH were performed in 11 247 individual patients at 88 hospitals (Figure 1). Of these cases, 1798 procedures were excluded because the subject was >21 years of age, 135 procedures were excluded because the patient was receiving ECMO, 32 procedures were excluded because the patient was using a left ventricular assist device, 1214 cases were excluded because the patient had a single-ventricle physiological feature, and 1765 cases were excluded because the pulmonary/systemic blood flow ratio was >1.5:1 and the PVRI was <4 WU/m². A total of
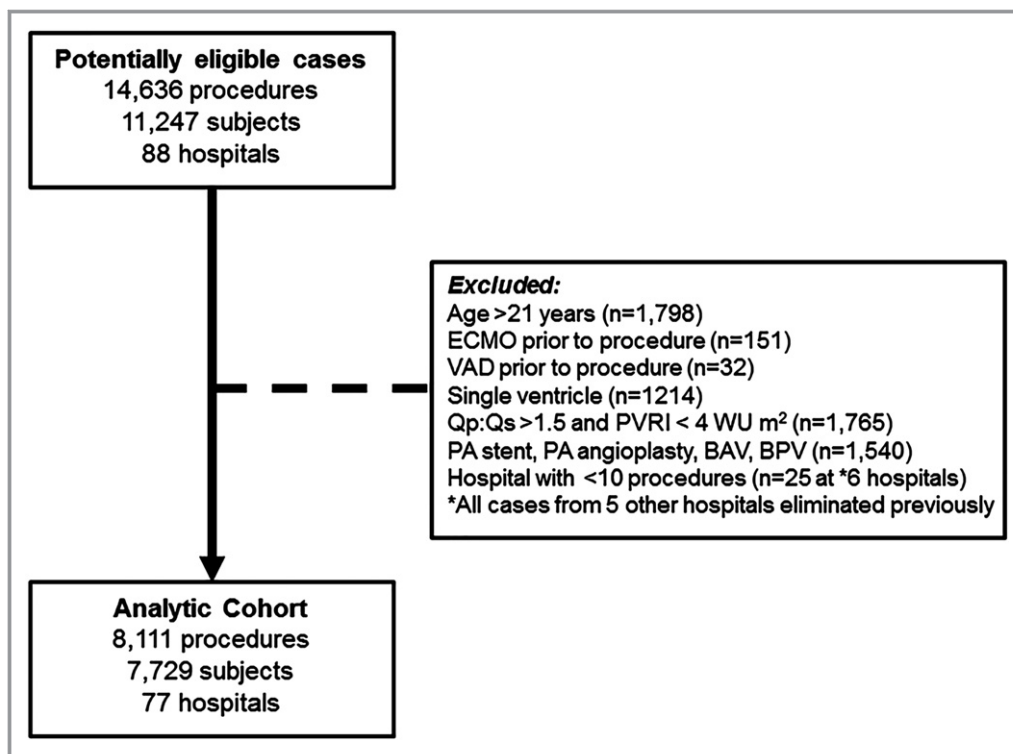
Figure 1. Study population. BAV indicates balloon aortic valvuloplasty; BPV, balloon pulmonary valvuloplasty; ECMO, extracorporeal membrane oxygenation; PA, pulmonary artery; PVRI, indexed pulmonary vascular resistance; Qp:Qs, ratio of pulmonary/systemic blood flow; and VAD, ventricular assist device.

1540 cases for PA stent or balloon angioplasty, aortic valvuloplasty, and pulmonary valvuloplasty were excluded. Excluding these cases removed all the cases from 5 hospitals. An additional 6 hospitals (and 25 cases) were excluded because of <10 procedures during the study period. The resulting analytic cohort included 8111 procedures performed in 7729 patients at 77 hospitals. This represents 10.5% (9010/77 116) of all procedures in the IMPACT registry during the study period.

Median age at catheterization was 3 years (IQR, 0–12 years) (Table 1). Of catheterizations, 51% were performed in subjects who were men and 64% in white subjects. In terms of diagnosis, 26% occurred in subjects with IPAH, 45% occurred in those with PH associated with congenital heart disease, 17% occurred in those with PH after an orthotopic heart transplant, 7% occurred in those with PH and cardiomyopathy, and 6% occurred in those with pulmonary vein pathology. A history of chronic lung disease was present in 21% of subjects. Renal insufficiency was known in 4.2% of subjects. Before catheterization, 21% received antihypertensive medications (including calcium channel blockers), 25% received vasodilators, and 12% received inotropes. Of the total cases, 14% were mechanically ventilated before the procedure; 2.6% had undergone a cardiac operation in the 30 days before catheterization.

General anesthesia was used in 85% of cases (Table 2). Of the total cases, 62% were intubated at the start of the case, 10% were previously intubated, 8% received a laryngeal mask airway, and 4% had a previous tracheostomy. Of procedures, 26% included a transcatheter intervention (Table 3).

Mean cardiac index was 3.8 ± 1.4 L/min per m^2. Median PVRI was 4.1 WU/m^2 (IQR, 2.6–6.5 WU/m^2), with 67% of cases performed in subjects with PVRI >3 WU/m^2. Hemodynamic vulnerability was present in 76% of subjects, 55% if excluding PVRI.

Outcomes

Observed risk of catastrophic event was 1.4% (95% CI, 1.2%–1.7%) (Table 4). The risk of death in the catheterization laboratory was 0.1%, the risk of cardiac arrest was 1.2%, initiation of ECMO was 0.4%, and death within 1 day of catheterization was 0.4%. Observed risk of death before discharge was 5.2%. The risk of any major adverse event, excluding death, was 5.0%. Including death before discharge, the risk was 9.1%. The median postprocedure hospital length of stay was 1.0 day (IQR, 0–10 days).

Multivariable Model

A multivariable model was calculated to assess the association between patient-level characteristics and risk of catastrophic adverse event (Figure 2). The odds ratio (OR) for catastrophic adverse event was greater in premature neonates (OR, 3.89; 95% CI, 1.17–12.89; P=0.03) and infants without prematurity (OR, 1.72; 95% CI, 1.04–2.83; P=0.03) than in subjects between 1 and 8 years old. The receipt of inotropes before the procedure was associated with increased risk (OR, 7.23; 95% CI, 4.77–10.96; P<0.0001). Increasing systemic arterial saturation was associated with a lower OR (OR, 0.81 per 5% change; 95% CI, 0.74–0.89; P<0.0001). Using conditional standardization, the risk of catastrophic adverse event in a patient with idiopathic pulmonary arterial hypertension between 1 and 8 years old, with no additional risk factors, is 0.9%.

A sensitivity analysis was performed that restricted cases to the first catheterization for each individual patient (Table S2). There were no significant changes in the observed association between risk factors and outcome, supporting the notion that including multiple catheterizations for individual subjects did not bias results.

Severity of PH and Risk

The associations between risk of composite outcome and 3 hemodynamic markers (mean PA pressure, PVRI, and cardiac index) were evaluated in separate models (Tables S3 through S5). Increasing PA pressure (OR, 1.21 per 10 mm Hg; 95% CI, 1.11–1.32 per 10 mm Hg; P<0.0001) and PVRI (OR, 1.08 per 1 WU/m^2; 95% CI, 1.05–1.11 per 1 WU/m^2; P<0.0001) were both associated with a higher OR for catastrophic adverse event, whereas a higher cardiac index was associated with a lower OR for catastrophic adverse event (OR, 0.75 per 1 L/min per m^2 increase; 95% CI, 0.63–0.90 per 1 L/min per m^2 increase; P=0.002).

Effect of Procedural Volume

In the study sample, the median annual hospital total catheterization volume was 266 cases (IQR, 145–445 cases). For the same sample, the median number of PH cases each year was 25 (IQR, 15–47). The median proportion of catheterizations performed in subjects with PH was 10% (IQR, 9%–12%; range, 4%–21%). For each center, the number of catheterizations in subjects with PH was proportional to the total number of catheterizations performed and correlated significantly to the total catheterization volume, although there remains significant variation between centers (β, 0.16; P<0.0001; r^2=0.86; Figure 3).

To assess whether procedural volume affected the risk of catastrophic adverse event, a secondary analysis was performed, adding the total catheterization and PH catheterization volumes to the model including PVRI (Table S6). Increasing annual PH volume was associated with a lower

Table 1. Study Population

Variable	Value
No. of catheterization procedures	8111
No. of individual patients	7729
No. of sites	77
Age, mean (IQR), y	3 (0–12)
Age category	
Neonate with prematurity	0.6 (47)
Neonate without prematurity	2.7 (222)
Infant with prematurity	9.6 (780)
Infant without prematurity	14.3 (1162)
1–8 y	37.9 (3072)
8–18 y	30.2 (2453)
>18 y	4.6 (375)
Female sex	50 (4037)
Race	
White	64 (5194)
Black	21 (1692)
Asian	5 (437)
Other	10 (788)
Weight, mean (IQR), kg	14.6 (7.1–41.7)
Diagnosis	
APAH-CHD	45 (3615)
IPAH	26 (2135)
Status after OHT	17 (1339)
Cardiomyopathy	7 (553)
PV stenosis	6 (469)
Genetic syndrome	
None	87 (7061)
Alagille syndrome	0.4 (36)
22q11.2 Microdeletion syndrome	3 (241)
Trisomy 21	8 (674)
Williams-Beuren syndrome	0.5 (41)
Other genetic syndrome	0.7 (58)
Chronic lung disease	21 (1713)
Congenital diaphragmatic hernia	1.8 (143)
Renal insufficiency	4.2 (341)
Coagulation disorder	1.5 (120)
Diabetes mellitus	1.5 (123)
Hepatic disease	2.0 (164)
Seizure disorder	3.5 (279)
Sickle-cell anemia	0.5 (43)
Mechanical ventilation before catheterization	14 (1173)

Table 1. Continued

Variable	Value
Medications before catheterization	
Antiarrhythmic	6 (512)
Anticoagulation	10 (773)
Antihypertensive	21 (1721)
Antiplatelet	21 (1695)
β Blocker	7 (585)
Diuretics	43 (3510)
Pressors	12 (1005)
Vasodilators	25 (2049)
Case status	
Elective	80 (6452)
Urgent	18 (1444)
Emergency	2 (150)
Salvage	0.1 (11)
Cardiothoracic operation in prior 30 d	3 (210)

Data are given as percentage (number) unless otherwise indicated. APAH-CHD indicates pulmonary hypertension associated with congenital heart disease; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; OHT, orthotopic heart transplantation; and PV, pulmonary vein.

OR for catastrophic adverse event (OR, 0.84; 95% CI, 0.75–0.94; *P*=0.002). In the same model, increasing annual catheterization volume was associated with a higher OR of catastrophic adverse event (OR, 1.16; 95% CI, 1.04–1.30; *P*=0.007). The addition of these factors to the model does not affect the previously observed associations between risk factors and risk of catastrophic event. An additional model without PVRI included (but also including procedural volumes) was also calculated (Table S7), in which point estimates for coefficients and CIs did not differ significantly.

Discussion

This multicenter, retrospective, cohort study investigated the risk of catastrophic adverse events during and after cardiac catheterization in children and adolescents with PH. The observed risk of catastrophic adverse event (death, cardiac arrest, or initiation of ECMO) was 1.4%. To adjust for the specific case mix of this study, we also calculated an estimated risk (adjusting for known confounders and standardized for a school-aged child with IPAH), which was 0.9%. Both the observed and estimated risks for catastrophic adverse events are many-fold higher than those measured in single-center case series[12,13] and catheterization registries.[16] However, they are consistent with the much higher risks reported in recent studies using either administrative[18] or

Table 2. Procedure Characteristics

Characteristics	Value
Transcatheter intervention	26 (2114)
Procedure risk category	
1	58 (4692)
2	27 (2154)
3	7 (536)
4	9 (728)
Sedation/anesthetic strategy	
General anesthesia	85 (6855)
Sedation	14 (1141)
None	1 (70)
Missing/other	0.6 (45)
Airway strategy	
Endotracheal intubation (before case)	10 (828)
Endotracheal intubation (at start of case)	62 (5059)
Laryngeal mask airway	8 (685)
Spontaneous breathing	15 (1213)
Tracheostomy	4 (345)
CPAP/bag mask ventilation	0.2 (13)
Trainee present	68 (5479)
Hemodynamics	
Cardiac index, L/min per m^2	3.8±1.4
Mixed venous saturation, %	67±10
Systemic arterial saturation, %	93±7
PVRI, mean (IQR), WU/m^2 (n=7593)	4.1 (2.6–6.6)
PA pressure mean, mm Hg	33.0±9.1
Systemic ventricular end-diastolic pressure, mmHg	13.5±6.5
Hemodynamic vulnerability (ANY)	77 (6274)
MV saturation <60%	21 (1612)
Systemic arterial saturation <95%	43 (3274)
Systemic ventricular EDP >18 mmHg	22 (1146)
PVRI >3 WU/m^2	67 (4493)
Hemodynamic vulnerability (excluding PVRI)	55 (4430)

Data are given as percentage (number) or mean±SD, unless otherwise indicated. CPAP indicates continuous positive airway pressure; EDP, end-diastolic pressure; IQR, interquartile range; MV, mixed venous; PA, pulmonary artery; and PVRI, indexed pulmonary vascular resistance.

Table 3. Transcatheter Interventions

Procedure	Value (N=2097)
Closure of patent ductus arteriosus	26 (553)
Pulmonary vein balloon angioplasty	16 (339)
Pulmonary vein stent angioplasty	4 (92)
Creation/augmentation of an atrial septal communication	8 (161)
Angioplasty of coarctation (with or without stent)	5 (107)
Closure of atrial septal defect	5 (104)
Transcatheter pulmonary valve replacement	2 (51)
Other procedures	33 (690)

Data are given as percentage (number). In some cases, >1 intervention was performed. These interventions are listed separately.

clinical registry data.[15] There is no controversy about the importance of hemodynamic evaluation in patients with PH, but data from these studies reiterate the risks associated with catheterization in this population and the potential benefit of identifying modifiable risk factors for an adverse event.

To our knowledge, the largest cohort study of pediatric patients with PH undergoing catheterization is the Tracking Outcomes in Pediatric Pulmonary Hypertension registry,

which includes data from 908 catheterizations in 472 individual patients treated between January 2018 and February 2012 at 31 centers in 19 countries. The observed risk of catastrophic adverse event (cardiac arrest, ECMO, or catheterization-associated death) in this population was between 0.6% and 1.7%.[15] General anesthesia was identified as highly correlated with adverse events. However, the low total number of events makes statistical adjustment impossible. This is important because it is not possible to adjust for case mix, which is especially relevant in this cohort, in whom the median PVRI was 15.5 WU/m^2, and because it is not possible to explore what factors influence the risk of adverse events. A contemporaneous study using administrative data from the PHIS database generated a larger study population and allowed for risk adjustment and the identification of factors associated with adverse events.[18] In this study, being a premature neonate, PH after heart transplantation, and preprocedure systemic vasodilators or hemodialysis were associated with increased risk of catastrophic event, whereas receipt of pulmonary vasodilators before catheterization and age 8 to 18 years were associated with decreased risk. A clear limitation of studies using administrative data is that not all potentially relevant clinical information is included in the registry. For example, there are no hemodynamic (pressure or oximetry) data included in PHIS, and there are limited data about specific cardiac diagnoses and procedures.

The current study addresses these concerns. The IMPACT registry was designed to capture the characteristics of patients undergoing catheterization and the procedures themselves. As a result, it contains much greater detail about patient and procedural factors that potentially influence periprocedural risk and has defined fields to capture hemodynamic data.[5] This allowed for us to evaluate risk factors in light of more accurate clinical data and to potentially explore the role of hemodynamics. In the current study, younger patient age (premature neonates and infants without

Table 4. Outcomes

Outcomes	Value, % (n)	95% CI
Catastrophic adverse event (cardiac arrest, ECMO, death within 1 d of catheterization)	1.4 (114)	1.2–1.7
Death in laboratory	0.1 (10)	0.06–0.2
Cardiac arrest	1.2 (95)	0.9–1.4
Initiation of ECMO	0.4 (36)	0.3–0.6
Death within 1 d of catheterization	0.4 (33)	0.3–0.6
Death before discharge	5.2 (460)	4.7–5.7
Arrhythmia receiving cardioversion	0.6 (51)	0.5–0.8
Arrhythmia receiving medication	1.2 (115)	1.0–1.4
Arrhythmia receiving temporary pacemaker	0.2 (19)	0.1–0.4
Tamponade	0.2 (14)	0.1–0.3
New dialysis	0.1 (8)	0.04–0.2
Unplanned cardiac surgery	0.4 (30)	0.2–0.5
Unplanned other surgery	0.4 (31)	0.3–0.5
Repeated catheterization	0.4 (29)	0.2–0.5
Any major adverse event, except death	5.0 (407)	4.6–5.5
Any major adverse event, including death	9.1 (742)	8.5–9.8
Hospital length of stay, mean (IQR), d	1.0 (0–10)	NA

Outcomes occurring in <0.1% of cases included air embolus (n=1), new heart valve regurgitation (n=2), initiation of ventricular assist device (n=2), unplanned vascular surgery (n=2), and embolic stroke (n=3). CI indicates confidence interval; ECMO, extracorporeal membrane oxygenation; and IQR, interquartile range.

prematurity relative to older patients) was associated with higher risk of catastrophic adverse event, as was the receipt of inotropic medications before catheterization. More important, the use of a clinical registry of patients undergoing catheterization produced a large sample of patients with a broad range of diagnoses, severity of disease (evinced by the range of PVRI), and comorbid conditions. Thus, the estimated risk from this sample (the risk calculated for a patient with median age and no other comorbidities) is representative of the "real-world" risk associated with cardiac catheterization of a standard-risk patient with PH.

Two secondary analyses were performed. The first aimed to assess whether disease severity affected the risk of adverse event. The initial model was established to assess preprocedural risk factors, and the only hemodynamic measure was oxygen saturation. However, determining how hemodynamic measures of severity of disease affected risk of adverse event was clearly important. To accomplish this, in secondary analyses, PA pressure, PVRI, and cardiac index were each added to the primary model. They were added in separate models because of likely colinearity. Increasing magnitude of either PA pressure or PVRI was associated with

increased risk of catastrophic adverse event, whereas increasing cardiac output was associated with reduced risk. To our knowledge, previous studies have not had sufficient statistical power to assess the association between disease severity and risk of adverse events with catheterization. Identification of cut points where increasing risk accelerates would allow for identification of a higher-risk stratum of patients and direction of additional resources to these patients. However, the total number of events in the study sample was too small to apply splines or other methods to assess for these cut points, highlighting the importance of continued accrual of large observational data sets to refine our understanding of the relationship between severity of illness and risk of catastrophic adverse event.

Next, the degree to which hospital catheterization experience (both in terms of total catheterization volume and volume of patients with PH specifically) influenced risk of catastrophic event was studied. Procedural volume has been associated with reduced risk of adverse event in the catheterization of children across a broad range of diagnoses.[17,22] In previous studies of catheterization of patients with PH, the study samples were too small (both in terms of the number of patients and hospitals) to perform an analysis adjusted for case-mix, but in a study using PHIS data, the observed rate of catastrophic adverse events was higher in low-volume centers than in higher-volume centers.[18] In the current study, experience with catheterization of patients with PH (as reflected in average PH catheterizations per year) was associated with reduced risk of catastrophic adverse event, independent of total catheterization volume and of PVRI and other patient factors. It is important to acknowledge that the increased PH volume represents the experience of the entire care team. This includes not only the interventional cardiologist but also catheterization laboratory staff, anesthesiologists, specialists in PH, critical care physicians, and nursing. It is not possible to retrospectively determine if the differences in event are attributable to transmissible best practices (at any of these levels of the healthcare team) or an intrinsic benefit of increased procedural volume. An important next step is to explore these differences in future studies. This is relevant because disseminating best practices and/or centralizing care of these patients may be challenging, but these factors are much more modifiable than intrinsic patient characteristics.

The IMPACT registry is well suited to generating a representative study sample, which is a complementary data source to clinical registries. First, the IMPACT registry includes data from a broad range of hospitals across the United States, including primary pediatric and general hospitals of all sizes. Disease-specific registries, on the other hand, are more likely to be based in centers of excellence. Second, at a patient level, consent is not required for inclusion in the IMPACT registry, and all consecutive cases are included.
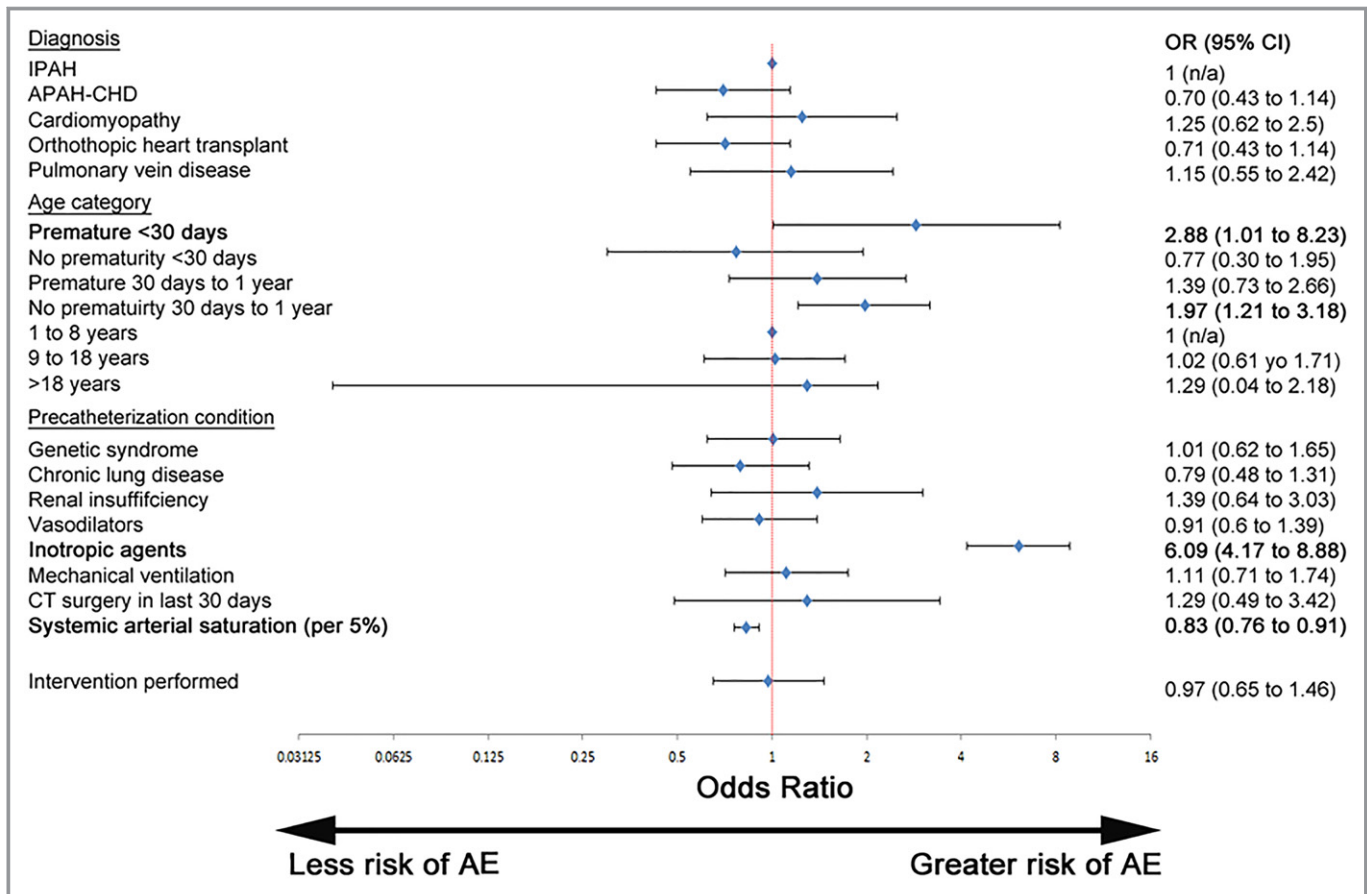
Figure 2. Risk factors for catastrophic adverse outcome. The figure is a forest plot that depicts the association between individual prespecified patient- and procedure-level factors potentially associated with the risk of death, cardiac arrest, or initiation of extracorporeal membrane oxygenation after catheterization in the study population. Odds ratios (ORs; blue diamonds) and 95% confidence intervals (CIs; brackets) are depicted from the mixed-effects multivariable model. For factors associated with increased risk of the composite outcome, the point estimate and 95% CI are completely to the right of the dashed line, marking an OR of 1. For factors associated with decreased risk of the composite outcome, the point estimate and 95% CI are entirely to the left of the dashed line. Factors with significant association to catastrophic adverse outcomes are boldfaced. AE indicated adverse event; APAH-CHD, pulmonary hypertension associated with congenital heart disease; CT, computed tomography; and IPAH, primary pulmonary hypertension.

Registries requiring consent are at risk for recruitment bias. Third, disease-specific registries may overemphasize a specific form of the disease. In PH-specific studies, this is manifest as overrepresentation of patients with IPAH in disease-specific studies. In large single-center series from PH centers and PH-specific registries, patients with IPAH represent 46% to 48% of procedures.[12,14,15,23] Studies that collect all catheterizations at a broad range of centers without consent have much lower prevalence of IPAH and with increased proportion of PH associated with congenital heart disease. This is seen in the current study, in which IPAH is less than a quarter of cases, and in studies using data from the PHIS database[18] and the Mid-Atlantic Group of Interventional Cardiology collaborative clinical registry.[16] PH centers likely see a larger proportion of patients with IPAH than other centers. This highlights that PH associated with congenital heart disease represents a larger proportion of the population

at risk across the country and that this population is potentially underrepresented in previous PH studies. Therefore, IMPACT and disease-specific registries fulfill complementary roles, with the IMPACT registry providing a representative national sample of broad practice, whereas disease-specific registries, such as the Tracking Outcomes in Pediatric Pulmonary Hypertension registry, summarize the results of elite centers in a narrower band of potentially severely ill patients.

An important potential modifiable factor for the safety of patients with PH undergoing cardiac catheterization is pharmacotherapy with pulmonary vasodilators. Medication has improved the survival of patients with PH. In our previous study using data from PHIS, patients receiving pulmonary vasodilators had a reduced risk of catastrophic adverse events with catheterization.[18] Although current recommendations are to pursue catheterization at diagnosis to test reactivity and
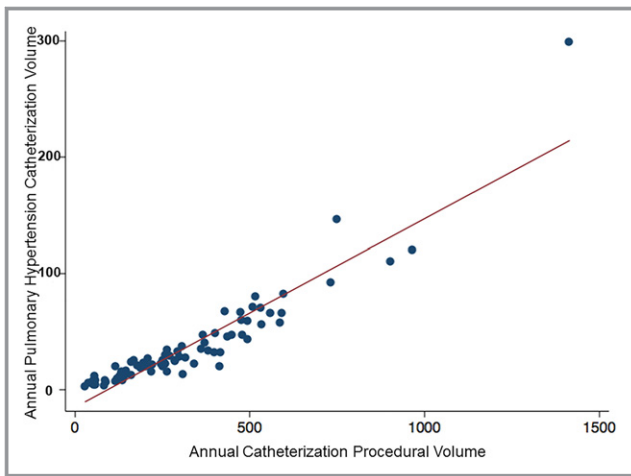
Figure 3. Relationship between hospital annual catheterization volume and annual volume of catheterizations performed in patients with pulmonary hypertension. The figure is a scatter plot of the average procedural volume for each hospital during the study period (each blue circle represents a contributing hospital). The total catheterization volume for each hospital is depicted on the x axis, and the number of cases performed per year in patients with pulmonary hypertension is depicted on the y axis. A line of best fit is plotted as well (red). Catheterizations performed in patients with pulmonary hypertension (PH) are a consistent proportion of total cases ($P<0.0001$ and $r^2=0.86$). PH catheterizations$=0.15\times$total catheterizations-15.

guide therapy,[4] there may be patients in whom initiating treatment before catheterization might mitigate risk without inducing harm. This has to be balanced against the potential risk of treatment without understanding the patient's physiological characteristics. We had hoped to further assess this association, but the current version of the IMPACT registry does not record specific preprocedural medications. Instead, medications are recorded according to 8 predefined categories (inotropes, vasodilators, antiarrhythmics, antiplatelet agents, anticoagulants, diuretics, β blockers, and blood pressure medications). There is no category for pulmonary vasodilators, and there is, thus, risk for omission or misclassification of these medications, making analysis of them impossible in this study. As the IMPACT registry matures and undergoes serial revision, inclusion of more detailed records of precatheterization medications would provide a more flexible structure for asking and answering clinically relevant questions. A potential work-around for this obstacle would be to create a link between the IMPACT registry and an administrative data set, such as PHIS, as has been modeled previously.[24] This leverages the strengths of both data sets, combining the detailed clinical information present in the former with detailed information about the use of medications[25,26] and other resources, including economic cost,[27] that are contained in the latter.

An important limitation to this study and observational studies in general is that they are limited in their scope to the current range of practice. Unless a practice is widespread and distributed across risk categories with sufficient overlap, it is not possible to determine if it affects outcome. The method chosen for airway management is an important practice in children with PH. Hypoventilation and resultant hypercarbia can precipitate a life-threatening pulmonary hypertensive crisis. Whether this is more likely with general anesthesia (with risks during induction and recovery) or with free breathing (with risk of respiratory suppression during the procedure, along with the potential for hemodynamic/autonomic instability) is not clear. In a prior study, use of general anesthesia had been associated with increased risk of adverse outcome.[15] In the current study, >80% of subjects had received anesthesia with positive pressure ventilation during the procedure. This preponderance makes statistical evaluation of other methods challenging. Moreover, it is also highly likely that individual choices of airway management were also determined by the care team and may correlate with preprocedural risk assessment (which would further contaminate any analyses). Without a broader range of practice, it is challenging to make inferences on the basis of the current data.

An important aspect of this study is that it reflects the burden of PH in a representative national sample of catheterization laboratories in the United States. When compared with PH-specific disease registries, such as the Tracking Outcomes in Pediatric Pulmonary Hypertension registry,[14,15] the mean PVRI and positive airway pressure are lower than in registries based in hospitals specializing in the care of patients with PH. This underscores both the excellent results of these centers in performing many catheterizations in severely ill patients and the importance of identifying the practices that enable them to do this. At the same time, the fact that the study sample includes many patients with relatively mild disease also means that the observed risk of major adverse events is a low-bound estimate.

There are several additional limitations to this study. First, the study is an observational study of current practice of patients undergoing catheterization. There is no means of identifying patients with prevalent PH who do not undergo catheterization, although it is not clear what the case mix of this population is relative to those who are undergoing catheterization. Also, in an observational study, one cannot infer causation from observed associations. In addition, the causes of PH are not recorded directly in the IMPACT registry in all cases. As described in the Methods section, these distinctions were made using a combination of diagnostic codes and hemodynamic data. This also complicates interpretation of the association between systemic

arterial saturation and the risk of adverse outcome. Also, the study population contains a larger proportion of patients with PH associated with congenital heart disease than with chronic lung disease, but we do not have the ability to determine if desaturation attributable to lung disease and that from right-to-left shunt is equally associated with adverse outcome. Third, attributing even catastrophic adverse outcomes in sick patients to the catheterization is challenging.[17,18,28] Restriction of the primary outcome to unequivocal events that might be plausibly related to PH was performed. In addition, where possible, the time horizon was limited to improve the attributability. Finally, subjects in this series underwent multiple catheterizations. This poses 2 problems. First, patients can undergo multiple catheterizations either by routine or because of increased severity of illness. Second, and more important, in an analysis in which the outcome is a catastrophic adverse outcome, patients who undergo multiple catheterizations do not face the same risk at each catheterization. By definition, they have not died at previous catheterizations. As in previous analyses,[17,18,22] we performed a sensitivity analysis restricted to the initial catheterization to demonstrate that the inclusion of repeated catheterizations did not bias our results significantly.

Conclusion

Despite these limitations, we conclude that catheterization in children with PH demonstrated a relatively high risk of catastrophic adverse outcome. Risk is proportional to the severity of pulmonary vascular disease. Experience with catheterization in patients with PH was associated with a reduced risk. Further research is necessary to evaluate whether this association is attributable to transmissible best practices or an intrinsic result of procedural volume.

Sources of Funding

Disclosures

None.

References

1. van Loon RLE, Roofthooft MTR, Hillege HL, ten Harkel ADJ, van Osch-Gevers M, Delhaas T, Kapusta L, Strengers JLM, Rammeloo L, Clur SAB. Pediatric pulmonary hypertension in the Netherlands. *Circulation*. 2011;124:1755–1764.

2. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. *Heart*. 2010;96:1401–1406.

3. Fraisse A, Jais X, Schleich J-M, di Filippo S, Maragnès P, Beghetti M, Gressin V, Voisin M, Dauphin C, Clerson P, Godart FO, Bonnet D. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France. *Arch Cardiovasc Dis*. 2010;103:66–74.

4. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037–2099.

5. Jayaram N, Beekman RH, Benson L, Holzer R, Jenkins K, Kennedy KF, Martin GR, Moore JW, Ringel R, Rome J, Spertus JA, Vincent R, Bergersen L. Adjusting for risk associated with pediatric and congenital cardiac catheterization: a report from the NCDR IMPACT Registry. *Circulation*. 2015;132:1863–1870.

6. Bergersen L, Gauvreau K, Foerster SR, Marshall AC, McElhinney DB, Beekman RH, Hirsch R, Kreutzer J, Balzer D, Vincent J, Hellenbrand WE, Holzer R, Cheatham JP, Moore JW, Burch G, Armsby L, Lock JE, Jenkins KJ. Catheterization for congenital heart disease adjustment for risk method (CHARM). *JACC Cardiovasc Interv*. 2011;4:1037–1046.

7. Bergersen L, Gauvreau K, Marshall A, Kreutzer J, Beekman R, Hirsch R, Foerster S, Balzer D, Vincent J, Hellenbrand W, Holzer R, Cheatham J, Moore J, Lock J, Jenkins K. Procedure-type risk categories for pediatric and congenital cardiac catheterization. *Circ Cardiovasc Interv*. 2011;4:188–194.

8. Nykanen DG, Forbes TJ, Du W, Divekar AA, Reeves JH, Hagler DJ, Fagan TE, Pedra CA, Fleming GA, Khan DM, Javois AJ, Gruenstein DH, Qureshi SA, Moore PM, Wax DH; Congenital Cardiac Interventional Study Consortium (CCISC). CRISP: Catheterization RISk score for Pediatrics: a report from the Congenital Cardiac Interventional Study Consortium (CCISC). *Catheter Cardiovasc Interv*. 2015;87:302–309.

9. Kreutzer J. Catastrophic adverse events during cardiac catheterization in pediatric pulmonary hypertension may not be so rare. *J Am Coll Cardiol*. 2015;66:1270–1272.

10. Carmosino MJ, Friesen RH, Doran A, Ivy DD. Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. *Anesth Analg*. 2007;104:521–527.

11. Taylor CJ, Derrick G, McEwan A, Haworth SG, Sury MRJ. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. *Br J Anaesth*. 2007;98:657–661.

12. Zuckerman WA, Turner ME, Kerstein J, Torres A, Vincent JA, Krishnan U, Kerstein D, Rosenzweig EB. Safety of cardiac catheterization at a center specializing in the care of patients with pulmonary arterial hypertension. *Pulm Circ*. 2013;3:831–839.

13. Bobhate P, Guo L, Jain S, Haugen R, Coe JY, Cave D, Rutledge J, Adatia I. Cardiac catheterization in children with pulmonary hypertensive vascular disease. *Pediatr Cardiol*. 2015;36:873–879.

14. Beghetti M, Berger RMF, Schulze-Neick I, Day RW, Pulido T, Feinstein J, Barst RJ, Humpl T; on behalf of the TOPP registry investigators. Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice. *Eur Respir J*. 2013;42:689–700.

15. Beghetti M, Schulze-Neick I, Berger RMF, Ivy DD, Bonnet D, Weintraub RG, Saji T, Yung D, Mallory GB, Geiger R, Berger JT, Barst RJ, Humpl T; TOPP Investigators, Mattos S, Jing ZC, Han ZY, Sondergaard L, Jensen T, Levy M, Mebus S, Apitz C, Szatmari A, Ablonczy L, Milanesi O, Favero V, Pulido T, La Garza De P, Douwes JM, Brun H, Moll L, Michalak K, Kawalec W, Zuk M, Boillat MF, Olguntürk R, Kula SS, Alehan D, Day RW, Austin E, Moore DJ, Atz AM, Feinstein JA. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: insights from the Global TOPP Registry (Tracking Outcomes and Practice In Paediatric Pulmonary hypertension). *Int J Cardiol*. 2016;203:325–330.

16. Hill KD, Lim DS, Everett AD, Ivy DD, Moore JD. Assessment of pulmonary hypertension in the pediatric catheterization laboratory: current insights from the MAGIC registry. *Catheter Cardiovasc Interv*. 2010;76:865–873.

17. O'Byrne ML, Glatz AC, Shinohara RT, Jayaram N, Gillespie MJ, Dori Y, Rome JJ, Kawut S. Effect of center catheterization volume on risk of catastrophic

adverse event after cardiac catheterization in children. *Am Heart J*. 2015;169: 823–832.e5.

18. O'Byrne ML, Glatz AC, Hanna BD, Shinohara RT, Gillespie MJ, Dori Y, Rome JJ, Kawut SM. Predictors of catastrophic adverse outcomes in children with pulmonary hypertension undergoing cardiac catheterization: a multi-institutional analysis from the Pediatric Health Systems Database. *J Am Coll Cardiol*. 2015;66:1261–1269.

19. Messenger JC, Ho KKL, Young CH, Slattery LE, Draoui JC, Curtis JP, Dehmer GJ, Grover FL, Mirro MJ, Reynolds MR, Rokos IC, Spertus JA, Wang TY, Winston SA, Rumsfeld JS, Masoudi FA; NCDR Science and Quality Oversight Committee Data Quality Workgroup. The National Cardiovascular Data Registry (NCDR) data quality brief: the NCDR data quality program in 2012. *J Am Coll Cardiol*. 2012;60:1484–1488.

20. Moore JW, Vincent RN, Beekman RH, Benson L, Bergersen L, Holzer R, Jayaram N, Jenkins K, Li Y, Ringel R, Rome J, Martin GR; NCDR IMPACT Steering Committee. Procedural results and safety of common interventional procedures in congenital heart disease: initial report from the National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2014;64:2439–2451.

21. Vincent RN, Moore J, Beekman RH, Benson L, Bergersen L, Holzer R, Jayaram N, Jenkins K, Ringel R, Rome J, Martin GR. Procedural characteristics and adverse events in diagnostic and interventional catheterisations in paediatric and adult CHD: initial report from the IMPACT Registry. *Cardiol Young*. 2016;26:70–78.

22. Jayaram N, Spertus JA, O'Byrne ML, Chan PS, Kennedy KF, Bergersen L, Glatz AC. Relationship between hospital procedure volume and complications following congenital cardiac catheterization: a report from the IMproving Pediatric and Adult Congenital Treatment (IMPACT) registry. *Am Heart J*. 2017;183:118–128.

23. Douwes JM, Humpl T, Bonnet D, Beghetti M, Ivy DD, Berger RMF; TOPP Investigators. Acute vasodilator response in pediatric pulmonary arterial hypertension: current clinical practice from the TOPP registry. *J Am Coll Cardiol*. 2016;67:1312–1323.

24. Pasquali SK, Jacobs JP, Shook GJ, O'Brien SM, Hall M, Jacobs ML, Welke KF, Gaynor JW, Peterson ED, Shah SS, Li JS. Linking clinical registry data with administrative data using indirect identifiers: implementation and validation in the congenital heart surgery population. *Am Heart J*. 2010;160:1099–1104.

25. Pasquali SK, Li JS, He X, Jacobs ML, O'Brien SM, Hall M, Jaquiss RDB, Welke KF, Peterson ED, Shah SS, Jacobs JP. Comparative analysis of antifibrinolytic medications in pediatric heart surgery. *J Thorac Cardiovasc Surg*. 2012;143:550–557.

26. Pasquali SK, Li JS, He X, Jacobs ML, O'Brien SM, Hall M, Jaquiss RDB, Welke KF, Peterson ED, Shah SS, Gaynor JW, Jacobs JP. Perioperative methylprednisolone and outcome in neonates undergoing heart surgery. *Pediatrics*. 2012;129:e385–e391.

27. Pasquali SK, Jacobs ML, He X, Shah SS, Peterson ED, Hall M, Gaynor JW, Hill KD, Mayer JE, Jacobs JP, Li JS. Variation in congenital heart surgery costs across hospitals. *Pediatrics*. 2014;133:e553–e560.

28. Backes CH, Bergersen L, Rome JJ, Batlivala SP, Glatz AC, Ovunc B, David S, Rivera BK, Haque U, Kollins K, Yin H, Holzer RJ. Quality metrics in cardiac catheterization for congenital heart disease: utility of 30-day mortality. *Catheter Cardiovasc Interv*. 2015;85:104–110.

Supplemental Material

Covariate	OR	95% CI
Age category		
Neonate with prematurity	4.35	2.04-9.29
Neonate without prematurity	0.74	0.28-1.98
Infant with prematurity	1.16	0.53-2.53
Infant without prematurity	1.74	1.08-2.83
1-8 years	1	n/a
8-18 years	0.85	0.41-1.79
>18 years	0.24	0.03-1.76
Diagnosis		
IPAH	1	n/a
APAH-CHD	0.87	0.52-1.47
Status post OHT	1.25	0.55-2.82
Cardiomyopathy	0.99	0.51-1.93
PV stenosis	1.25	0.71-2.18
Genetic Syndrome	0.89	0.56-1.41
Chronic lung disease	0.91	0.54-1.54
Renal insufficiency	1.39	0.68-2.85
Pressors before catheterization	6.88	4.52-10.45
Vasodilators before catheterization	0.84	0.58-1.21
Mechanical ventilation	0.93	0.55-1.55
Cardiothoracic operation in last 30 days	1.23	0.51-2.97
Intervention performed	1.01	0.58-1.76
Systemic arterial saturation (increasing by 5%)	0.81	0.74-0.89

Supplementary Table 1: Generalized estimating equation model estimates of the risk of catastrophic adverse event

Abbreviations: APAH-CHD pulmonary hypertension associated with congenital heart disease, IPAH idiopathic pulmonary arterial hypertension, OHT orthotopic heart transplantation, PV pulmonary vein

Covariate	OR	95% CI
Age category		
Neonate with prematurity	4.14	1.25-13.75
Neonate without prematurity	0.78	0.25-2.39
Infant with prematurity	0.93	0.44-1.96
Infant without prematurity	1.59	0.94-2.70
1-8 years	1	n/a
8-18 years	0.92	0.54-1.57
>18 years	0.27	0.04-2.04
Diagnosis		
IPAH	1	n/a
APAH-CHD	0.87	0.52-1.47
Status post OHT	0.68	0.29-1.59
Cardiomyopathy	1.15	0.55-2.43
PV stenosis	1.32	0.58-2.99
Genetic Syndrome	0.82	0.46-1.46
Chronic lung disease	0.91	0.53-1.56
Renal insufficiency	1.73	0.79-3.80
Pressors before catheterization	6.73	4.36-10.37
Vasodilators before catheterization	0.86	0.54-1.35
Mechanical ventilation	0.88	0.52-1.49
Cardiothoracic operation in last 30 days	1.30	0.44-3.83
Intervention performed	1.08	0.66-1.78
Systemic arterial saturation (increasing by 5%)	0.84	0.76-0.93

Supplementary Table 2: Sensitivity analysis of risk factors for catastrophic adverse events restricted to the first catheterization during the study period for each subject

Abbreviations: APAH-CHD pulmonary hypertension associated with congenital heart disease, IPAH idiopathic pulmonary arterial hypertension, OHT orthotopic heart transplantation, PV pulmonary vein

Covariate	OR	95% CI
Indexed pulmonary vascular resistance (per 1 WU/m^2)	1.08	1.05-1.11
Age category		
Neonate with prematurity	3.06	0.59-15.93
Neonate without prematurity	0.72	01.6-3.26
Infant with prematurity	1.14	0.51-2.52
Infant without prematurity	1.55	0.85-2.83
1-8 years	1	n/a
8-18 years	0.56	0.31-1.03
>18 years	0.24	0.03-1.81
Diagnosis		
IPAH	1	n/a
APAH-CHD	1.17	0.64-2.13
Status post OHT	1.16	0.45-2.95
Cardiomyopathy	1.92	0.83-4.44
PV stenosis	1.11	0.43-2.87
Genetic Syndrome	0.65	0.31-1.35
Chronic lung disease	0.80	0.44-1.45
Renal insufficiency	1.75	0.73-4.21
Pressors before catheterization	6.24	3.84-10.14
Vasodilators before catheterization	0.89	0.54-1.48
Mechanical ventilation	0.99	0.56-1.77
Cardiothoracic operation in last 30 days	1.87	0.62-5.67
Intervention performed	1.59	0.92-2.77
Systemic arterial saturation (increasing by 5%)	0.85	0.75-0.97

Supplementary Table 3: Association between indexed pulmonary vascular resistance and risk of catastrophic adverse events

Abbreviations: APAH-CHD pulmonary hypertension associated with congenital heart disease, IPAH idiopathic pulmonary arterial hypertension, OHT orthotopic heart transplantation, PV pulmonary vein, WU Woods Unit

Covariate	OR	95% CI
Mean pulmonary artery pressure (per 10 mmHg)	1.21	1.11-1.32
Age category		
Neonate with prematurity	5.92	1.72-20.39
Neonate without prematurity	0.96	0.31-2.96
Infant with prematurity	0.99	0.45-2.18
Infant without prematurity	2.07	1.22-3.51
1-8 years	1	n/a
8-18 years	0.87	0.50-1.53
>18 years	0.25	0.04-2.29
Diagnosis		
IPAH	1	n/a
APAH-CHD	0.86	0.50-1.49
Status post OHT	1.23	0.53-2.84
Cardiomyopathy	1.98	0.92-4.26
PV stenosis	0.88	0.37-2.08
Genetic Syndrome	0.99	0.56-1.75
Chronic lung disease	0.91	0.52-1.59
Renal insufficiency	1.50	0.68-3.32
Pressors before catheterization	6.19	3.97-9.66
Vasodilators before catheterization	0.68	0.42-1.10
Mechanical ventilation	0.97	0.58-1.63
Cardiothoracic operation in last 30 days	1.23	0.41-3.69
Intervention performed	1.16	0.70-1.91
Systemic arterial saturation (increasing by 5%)	0.85	0.76-0.94

Supplementary Table 4: Association between mean pulmonary artery pressure and risk of catastrophic adverse events

Abbreviations: APAH-CHD pulmonary hypertension associated with congenital heart disease, IPAH idiopathic pulmonary arterial hypertension, OHT orthotopic heart transplantation, PV pulmonary vein

Covariate	OR	95% CI
Cardiac index (per L/min/sqm)	0.75	0.63-0.90
Age category		
Neonate with prematurity	3.30	0.84-13.03
Neonate without prematurity	0.69	0.20-2.45
Infant with prematurity	1.01	0.49-2.08
Infant without prematurity	1.24	0.71-2.17
1-8 years	1	n/a
8-18 years	0.66	0.37-1.17
>18 years	0.21	0.03-1.62
Diagnosis		
IPAH	1	n/a
APAH-CHD	0.77	0.45-1.32
Status post OHT	0.63	0.27-1.45
Cardiomyopathy	0.91	0.42-1.99
PV stenosis	0.95	0.40-2.24
Genetic Syndrome	0.71	0.38-1.33
Chronic lung disease	0.85	0.49-1.47
Renal insufficiency	1.79	0.81-3.98
Pressors before catheterization	6.83	4.34-10.74
Vasodilators before catheterization	0.72	0.44-1.16
Mechanical ventilation	0.99	0.59-1.68
Cardiothoracic operation in last 30 days	1.30	0.44-3.88
Intervention performed	1.39	0.82-2.35
Systemic arterial saturation (increasing by 5%)	0.76	0.68-0.84

Supplementary Table 5: Association between cardiac index and risk of catastrophic adverse events

Abbreviations: APAH-CHD pulmonary hypertension associated with congenital heart disease, IPAH idiopathic pulmonary arterial hypertension, OHT orthotopic heart transplantation, PV pulmonary vein

Covariate	OR	95% CI
Annual PH catheterization volume (per 10 cases)	0.84	0.75-0.94
Annual catheterization volume (per 50 cases)	1.16	1.04-1.30
Age category		
Neonate with prematurity	3.10	0.60-16.08
Neonate without prematurity	0.71	0.16-3.20
Infant with prematurity	1.14	0.52-2.53
Infant without prematurity	1.49	0.82-2.72
1-8 years	1	n/a
8-18 years	0.56	0.30-1.02
>18 years	0.23	0.03-1.75
Diagnosis		
IPAH	1	n/a
APAH-CHD	1.17	0.64-2.13
Status post OHT	1.16	0.46-2.94
Cardiomyopathy	1.95	0.84-4.50
PV stenosis	1.16	0.45-2.99
Indexed pulmonary vascular resistance (per 1 WU/sqm)	1.08	1.05-1.11
Genetic Syndrome	0.65	0.31-1.34
Chronic lung disease	0.78	0.43-1.40
Renal insufficiency	1.69	0.70-4.07
Pressors before catheterization	6.48	4.00-10.50
Vasodilators before catheterization	0.88	0.53-1.45
Mechanical ventilation	1.02	0.57-1.82
Cardiothoracic operation in last 30 days	1.84	0.51-5.53
Intervention performed	1.64	0.95-2.83
Systemic arterial saturation (increasing by 5%)	0.86	0.76-0.97

Supplementary Table 6: Association between total annual catheterization volume and pulmonary hypertension case volume and risk of catastrophic adverse events

Abbreviations: APAH-CHD pulmonary hypertension associated with congenital heart disease, IPAH idiopathic pulmonary arterial hypertension, OHT orthotopic heart transplantation, PV pulmonary vein

Covariate	OR	95% CI
Annual PH catheterization volume (per 10 cases)	0.89	0.82-0.97
Annual catheterization volume (per 50 cases)	1.11	1.01-1.22
Age category		
Neonate with prematurity	3.87	1.18-12.75
Neonate without prematurity	0.70	0.23-2.13
Infant with prematurity	1.12	0.57-2.21
Infant without prematurity	1.68	1.02-2.77
1-8 years	1	n/a
8-18 years	0.81	0.48-1.38
>18 years	0.24	0.03-1.81
Diagnosis		
IPAH	1	n/a
APAH-CHD	0.79	0.48-1.29
Status post OHT	0.73	0.31-1.59
Cardiomyopathy	1.25	0.62-2.52
PV stenosis	1.18	0.54-2.61
Genetic Syndrome	0.88	0.51-1.51
Chronic lung disease	0.86	0.52-1.44
Renal insufficiency	1.39	0.64-3.06
Pressors before catheterization	7.44	4.92-11.26
Vasodilators before catheterization	0.74	0.48-1.15
Mechanical ventilation	0.90	0.55-1.46
Cardiothoracic operation in last 30 days	1.12	0.38-3.27
Intervention performed	1.09	0.68-1.74
Systemic arterial saturation (increasing by 5%)	0.82	0.74-0.90

Supplementary Table 7: Association between total annual catheterization volume and pulmonary hypertension case volume and risk of catastrophic adverse events (PVRI removed from the model)

Abbreviations: APAH-CHD pulmonary hypertension associated with congenital heart disease, IPAH idiopathic pulmonary arterial hypertension, OHT orthotopic heart transplantation, PV pulmonary vein