

Pediatric and Adolescent Pulmonary Hypertension: What Is the Risk of Undergoing Invasive Hemodynamic Testing?

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Pediatric pulmonary hypertension (PH) is a complex disease associated with significant morbidity and mortality. Important pediatric PH subtypes include the following: idiopathic pulmonary arterial hypertension (IPAH), PH associated with congenital heart disease, and PH secondary to lung disease. PH-targeted medications have led to improved survival; in children who did not respond to a calcium channel blocker at heart catheterization (HC), the 4-year survival without directed pulmonary arterial hypertension therapy was poor (35%)¹ compared with a 5-year survival of 84% in children receiving PH-specific medical therapy.² Children with PH are considered high risk for invasive procedures and surgery, given that life-threatening complications, such as PH crisis, can occur. In PH crisis, the pulmonary vascular resistance (PVR) immediately increases to a point at which pulmonary artery pressure exceeds systemic arterial pressure, resulting in reduced pulmonary perfusion and subsequent decline in cardiac output, followed by hypoxia and biventricular failure. Common precipitants of PH crisis are as follows: infection, malfunction of pump/catheter infusing prostacyclin analog therapy, pulmonary embolism, arrhythmia, trauma, anemia, and worsening hypoxia.

Hemodynamic assessment with HC is the standard tool used to evaluate hemodynamics at presentation and in reassessment after targeted therapy.³ The overall adverse

event (AE) rate with pediatric HC is relatively low at 0.1%⁴; however, HC in children with PH is substantially higher, with cardiac arrest occurring in 4% to 6%.^{5,6}

Both single-center and pooled registry data have shown that children with PH undergoing HC have a high risk of major AEs (3.5%–6.2%) and death (0.2%–1.4%).^{4,6–14} However, there are limited data identifying important risk factors for major AE and death in the pediatric PH population. Younger age, preprocedural systemic vasodilator use, renal dysfunction, higher mean pulmonary artery (mPA) pressure, single ventricle anatomy, and cardiac operation during the same admission have all been shown to be important risk factors for AE in pediatric and adolescent HC (Table). Prior studies have several limitations: small individual center volumes are not powered to be able to determine cutoff values for risk factors, databases that require consent are prone to recruitment bias, administrative databases have limited clinical data, and disease-specific registries may overrepresent a specific type of disease.

To more specifically estimate individual risk on the basis of PH severity, O'Byrne and colleagues, in this issue of *Journal of the American Heart Association (JAHA)* query the Improving Pediatric and Adult Congenital Treatment Registry to determine the risk of catastrophic AEs in children and adolescents with PH undergoing HC.¹⁵ A secondary analysis was undertaken to determine if PH disease severity affects individual AE risk and also to determine the degree to which hospital PH-HC experience affects AE risk. In patients 0 to 21 years of age, there were 8111 procedures (7729 subjects; 77 centers) between the years 2011 and 2015 (median age, 3 years [interquartile range, 0–12 years]; and median PVR Index, 4.1 WU/m² [interquartile range, 2.6–6.5 WU/m²]). Subjects were included if they had ≥ 1 of following diagnostic codes or met ≥ 1 of the following criteria: IPAH, pulmonary vascular obstructive disease, mPA pressure >25 mm Hg, or PVR Index >4 WU/m². Exclusion criteria included the following: elevated mPA pressure without elevated PVR Index attributable to left-to-right shunt, fixed anatomic stenosis undergoing PA angioplasty or pulmonary valvuloplasty, centers with <10 PH catheterizations, patients receiving extracorporeal membrane oxygenation or left ventricular assist device therapy, and those with single-ventricle disease. The most common

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Table. Studies Evaluating Pediatric HC Risk

Author	Study Population	Outcomes and Risk Factors
O'Byrne et al, 2015 ^{4,11*}	<ol style="list-style-type: none"> Age: ≤21 y Source: PHIS Years: 2007–2012 Outcomes assessed: death and/or MCS 6339 procedures; 4401 patients; 38 centers¹¹ 63 994 procedures; 40 612 patients; 38 centers⁴ 	<ol style="list-style-type: none"> Observed AE rate: 3.5% (n=222)¹¹ Adjusted AE rate: 3.3%¹¹; 0.1%⁴ Mortality risk: 0.3% (n=17)¹¹ ↑ HC (OR, 0.78 per 100 HCs)⁴ Pulmonary vasodilator therapy (OR, 0.38)¹¹ Risk factors (OR)¹¹: prematurity (4.95), infants without prematurity (1.61), cardiac surgery during the same admission, prior heart transplantation (2.78), hemodialysis (19.40)
Beghetti et al, 2016 ^{7*}	<ol style="list-style-type: none"> Age: 3 mo to 18 y Source: TOPP Years: 2008–2012 Outcomes assessed: AEs and death 908 procedures, 472 patients; 31 centers 	<ol style="list-style-type: none"> AE rate: 5.9% (n=54) Mortality risk: 0.6% (n=5) Risk factors: GA, FC 3–4 (associated with ↑ mPAP)
Bergersen et al, 2011 ¹³	<ol style="list-style-type: none"> Age: ≤18 y Source: C3PO Years: 2007–2009 Outcomes assessed: AEs 9362 procedures; 8 centers 	<ol style="list-style-type: none"> AE rate: 5% (n=454) Risk factors (OR): EDP ≥18 mm Hg (1.8), SA sat <95%; SV sat <78% (1.9), MV sat <60%; SV sat <50% (2.6), PASP ≥45 mm Hg (2.7), mPAP ≥17 mm Hg if SV (2.0), RV ratio ≥0.4 non-SV (2.0)
Bobhate et al, 2015 ^{8*}	<ol style="list-style-type: none"> Age: 3 mo to 17 y Source: retrospective clinical data Years: 2009–2014 Outcomes assessed: AEs 97 procedures; 75 patients 	<ol style="list-style-type: none"> AE rate: 6.2% (n=6) Major AE rate: 3.1% (n=3) Minor AE rate: 3.1% (n=3) Risk factors: FC 3–4, suprasystemic PH, RV dysfunction, no PH therapy, PACI ≤1 mL/mm Hg per m²
Carmosino et al, 2007 ^{9*}	<ol style="list-style-type: none"> Age: 4 d to 30 y (median, 4 y) Source: retrospective clinical data Years: 1999–2004 Outcomes assessed: AEs (surgery/catheterization) 256 procedures; 55% HCs; 156 patients 	<ol style="list-style-type: none"> Major AE rate: 5.0% (n=7) of HC Minor AE rate: 3.1% (n=8) of HC PH crisis rate: 4.3% (n=6) of HC Mortality risk with HC: 1.4% (n=2) Risk factor: suprasystemic PH (OR, 8.1)
Hill et al, 2010 ^{10*}	<ol style="list-style-type: none"> Age: ≤18 y Source: MAGIC Years: 2003–2008 Outcomes assessed: AEs 177 procedures; 7 centers 	<ol style="list-style-type: none"> AE rate: 3.9% (n=7) Risk factors: baseline mPAP, percentage systemic PAP
Jayaram et al, 2015 ⁵	<ol style="list-style-type: none"> Age: neonate-adulthood Source: IMPACT Years: 2011–2013 Outcomes assessed: AEs 19 608 procedures 	<ol style="list-style-type: none"> Major AE rate: 1.9% (n=378) Risk factors (OR): renal insufficiency (4.89), single ventricle (1.40), systemic sat ≤95% (non-SV) or ≤78% (SV) (1.05), MV sat <60% (non-SV) or <50% (SV) (2.56), EDP ≥18 mm Hg (1.31), mPAP ≥17 mm Hg (SV) or PASP ≥45 mm Hg (non-SV) (2.73)
Nykanen et al, 2016 ¹⁴	<ol style="list-style-type: none"> Age: ≤18 y Source: CCISC Years: 2008–2013 Outcomes assessed: serious AEs and death 14 790 procedures; 20 centers 	<ol style="list-style-type: none"> AE rate: 4.5% (n=665 procedures; 1072 patients) Mortality risk with HC: 0.08% (n=12) Risk factors: patient status (emergent/urgent), age (<30 d), weight (<2.5 kg), inotrope use, respiratory failure on mechanical ventilation, systemic illness/failure, physiologic category,¹⁴ precatheterization diagnosis risk stratification,¹⁴ ASA score

Continued

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Author	Study Population	Outcomes and Risk Factors
Taylor et al, 2007 ^{6*}	<ol style="list-style-type: none"> Age: ≤18 y Source: retrospective clinical data Years: 1999–2004 Outcomes assessed: AEs and death 94 procedures; 70 patients 	<ol style="list-style-type: none"> Overall serious AE rate (resuscitation or death): 6% (n=4) Serious AE rate in PPH: 13% (n=3) Cardiac arrest rate: 5.7% (n=6) Mortality risk: 1.4% (n=1) Risk factors: syncope, chest pain, TR velocity >4 m/s
Zuckerman, 2013 ^{12*}	<ol style="list-style-type: none"> Age: neonate-adulthood Source: retrospective clinical data Years: 2002–2012 Outcomes assessed: AEs and death 1637 procedures; 607 patients 50% pediatric patients with PH 	<ol style="list-style-type: none"> Overall AE rate: 5.7% (n=93) Major AE rate: 1.2% (n=20) Minor AE rate: 4.5% (n=73) Mortality rate: 8 deaths; 0.2% HC related (n=4) Risk factors (HR): age <2 y (8.08), APAH-CHD vs IPAH (1.57), GA (5.44), left HC (3.55), catheter-based intervention (3.07), ↑ RAP (1.07), ↑ PCWP (1.08)

↑ indicates increased; AE, adverse event; APAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; ASA, American Society for Anesthesia; C3PO, Congenital Cardiac Catheterization Project on Outcomes; CCISC, Congenital Cardiac Interventional Study Consortium; EDP, end diastolic pressure; FC, functional class; GA, gestational age; HC, heart catheterization; HR, hazard ratio; IMPACT, Improving Pediatric and Adult Congenital Treatment; IPAH, idiopathic pulmonary arterial hypertension; MAGIC, Mid-Atlantic group of interventional cardiology collaboration PH registry data set; MCS, mechanical circulatory support; mPAP, mean pulmonary arterial pressure; MV, mixed venous; OR, odds ratio; PACI, Pulmonary Artery Capacitance Index; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PHIS, Pediatric Health Information Systems Database; PPH, pediatric pulmonary hypertension; RAP, right atrial pressure; RV, right ventricle; SA, systemic arterial; Sat, saturation (%); SV, single ventricle; TOPP, tracking outcomes and practice in pediatric pulmonary hypertension; and TR, tricuspid regurgitation.

*Indicates patient population in the study was PH specific.

diagnoses in those included for analysis were PH associated with congenital heart disease (46%), IPAH (26%), and PH after orthotopic heart transplant (17%).

Catastrophic AEs included death up to 24 hours after catheterization, cardiac arrest, and/or initiation of extracorporeal membrane oxygenation within 30 days. The raw observed risk for catastrophic AEs was 1.4%, and the adjusted risk was 0.9%. The observed risk of death before discharge was 5.2%. This study provides new data showing several patient-level factors that increase risk with PH-HC: premature neonate (odds ratio [OR], 3.98), infant without prematurity (OR, 1.72), and pretreatment with inotropes (OR, 7.23). Higher systemic arterial saturation was protective of catastrophic AEs (OR, 0.81 per Δ5% saturation) as was higher cardiac index (OR, 0.75 per 1 L/min per m²). The degree of PH was also associated with higher catastrophic AE risk: PVR (OR, 1.08 per 1 WU/m²) and mPA pressure (OR, 1.21 per 10 mm Hg). Center PH-HC volume was also found to reduce risk of catastrophic AEs (OR, 0.84), yet it could not be determined if this was strictly because of increased procedural volume or overall center expertise in the treatment of PH. The main limitations in this study are that subjects had milder PH than in prior studies, data on upstream PH medications were not available (thereby limiting the ability to understand how specific targeted therapy affects risk/outcome with HC), and sample size limited the ability to report the magnitude of risk that PH severity plays in AEs.

Overall catastrophic AE risk in this study is similar to prior administrative and registry data sets. Important

information shown herein is that children with PH have similar HC risk factors for AEs, including premature neonates, term infants, and pretreatment with inotropes. Higher systemic arterial saturation and cardiac index were associated with lower AEs at the time of HC. These new data highlight that sequential increase in PVR or mPA pressure increases catastrophic AEs linearly. Center experience was also shown to affect catastrophic AE risk. Of the risk factors for development AEs in pediatric PH-HC identified in this study, only a few are potentially modifiable: pretreatment with inotropes, higher PVR, higher mPA pressure, and center experience. In the context of prior studies (Table), we propose that clinicians identify children with PH who are at higher risk for AEs and consider early expert PH evaluation to determine if up-front pulmonary vasodilator therapy, risk factor modification or avoidance of HC are reasonable to reduce AE risk (Figure). If possible, avoidance of general anesthesia or concurrent intervention during diagnostic HC are reasonable.

In conclusion, pediatric patients with PH have a higher AE risk when undergoing HC. The current study illustrates that the severity of PH linearly affects risk and that center experience matters. We propose early risk stratification and consideration of expert PH evaluation for those who are high risk, in addition to avoidance of general anesthesia and concurrent HC intervention, if possible. Further research aimed at refining individual risk assessment, including details about prior PH medical therapy, is needed to best risk stratify this population before invasive testing.

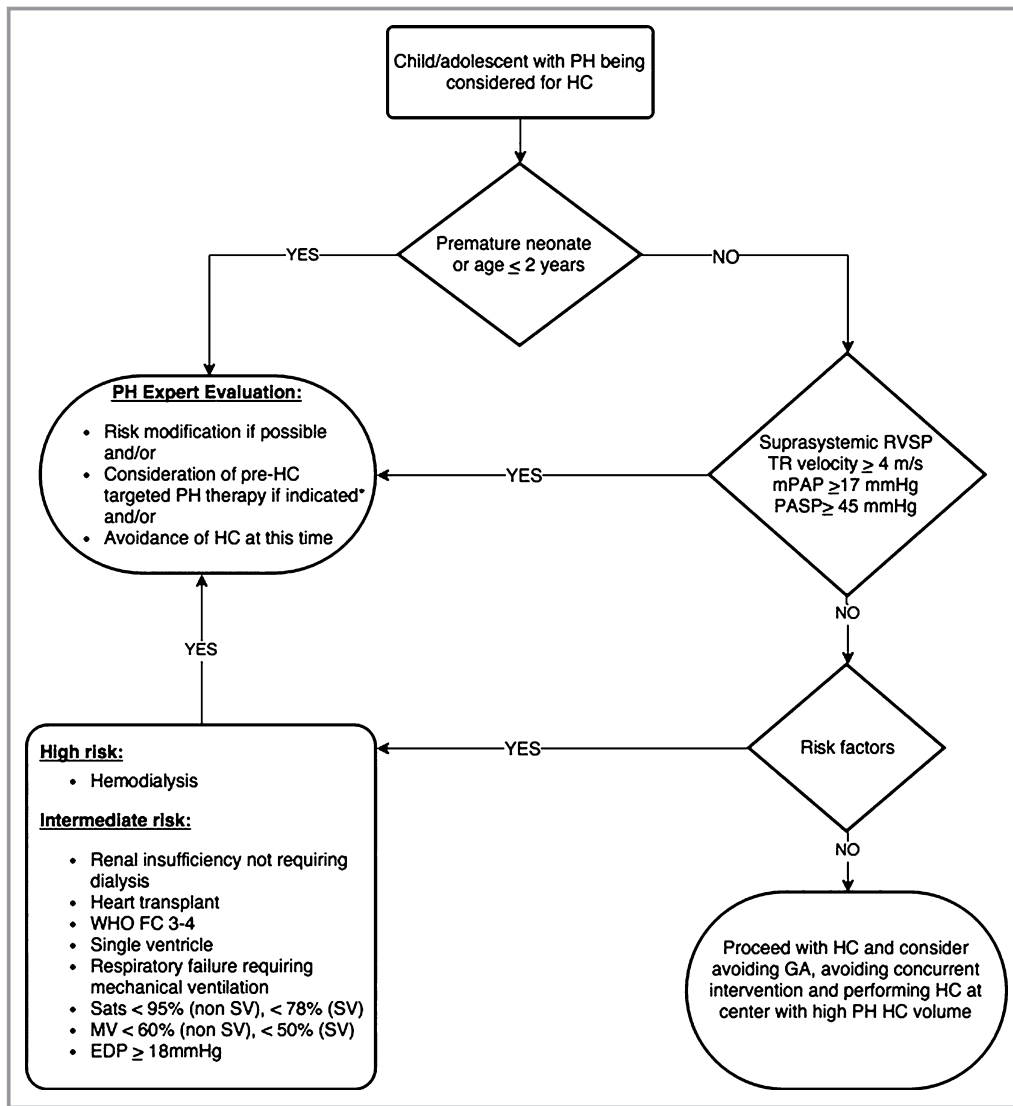


Figure. Pediatric pulmonary hypertension heart catheterization (PH-HC) risk. This algorithm represents one potential method to evaluate PH-HC risk in children; it is based on the findings in studies outlined in the Table and the current study by O’Byrne and colleagues.¹⁵ *We recommend that the institutional PH expert/team assess each patient where the decision tree leads to “consideration of pre-HC pulmonary vasodilator therapy.” The goal of this team is to determine if pre-HC pulmonary vasodilator therapy is required, and when indicated, to recommend the specific type of therapy on the basis of individual patient characteristics. EDP indicates end diastolic pressure; FC, functional class; GA, gestational age; mPAP, mean pulmonary artery pressure; MV, mixed venous; PASP, pulmonary artery systolic pressure; RVSP, right ventricular systolic pressure; Sat, saturation; SV, single ventricle; TR, tricuspid regurgitation (referring to jet velocity on ECG); and WHO, World Health Organization.

Disclosures

None.

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