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Reply: The Need for Comprehensive Cardiac Catheterization in Children With Pulmonary Hypertension: To "Cath" or Not in Pediatric Pulmonary Hypertension?

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We welcome the comments and interest of Doctors Hansmann and Apitz and Beghetti et al. We agree that cardiac catheterization is an essential component of the evaluation of pulmonary hypertension. Our study utilized administrative data from 38 children's hospitals in the United States to measure the risk of a catastrophic outcome using a standard definition(1) in children undergoing cardiac catheterization during inpatient and observation admissions. The use of administrative data overcomes the challenge of studying low event rates in a rare condition, and we included more than 6,000 procedures in 4,401 unique patients with a range of risk factors in our analysis. The data from TOPP were drawn from 31 centers in which 908 procedures were performed on 456 patients whose families provided informed consent. As acknowledged by the authors, patients who died may not have been included in the TOPP registry due to the absence of informed consent(2). Our analysis is more reflective of current practice since it includes expert and non-expert centers, many more procedures, and a patient population with a broader range of severity of illness.

The TOPP study and single center studies cited in the letters are valuable because they include detailed data from highly experienced pediatric centers with a narrower range of conditions and illness severity. In the series from Bobhate, Zuckerman, and Beghetti(2–4) the 95% confidence intervals for observed risk of mortality are 0–3.7%, 0.2–1.0%, and 0.2–1.3%. The standardized risk of composite outcome in our study was slightly higher (3.3%, 95% CI: 1.9–5.5%). However, our primary outcome includes both death and initiation of ECMO, the latter of which is not described in the studies by Zuckerman and Beghetti and will result in a higher event rate. Moreover, we cite a standardized estimate representing the risk for a "standard-risk profile" patient (a school age patient with idiopathic pulmonary hypertension without other risk factors). Reporting observed risks without adjusting for known confounders risks bias and makes comparisons between series challenging.

We acknowledge the limitations of administrative data (i.e. reliance on billing codes and missing data), however our analysis also has several additional strengths. First, we accounted for the relatedness of procedures within the same individual. A patient who did "well" with

the first procedure will be more likely to undergo a second or third procedure, leading to a biased "healthier" population if this relatedness is not considered when analyzing multiple procedures. In TOPP and other studies, every procedure (even if performed on the same patient) was considered independently, which does not fulfill necessary assumptions underlying the analysis (independence of outcomes) and may lead to "overrepresentation" of lower-risk individuals. Second, our significantly larger study population allowed us to use multivariable analysis to adjust for confounders and provide standardized estimates, which were not calculated in the referenced studies.

We agree that there are benefits of cardiac catheterization in pulmonary hypertension and the possible advantages of performing these procedures in experienced centers. Large studies which include both expert and non-expert centers and inclusive cohorts of patients are the best chance to support this anecdotal impression, as our group has shown in previously(5). Indeed, our study showed for the first time that higher volume centers had significantly lower risks of adverse outcomes compared to lower volume centers in pediatric patients with pulmonary hypertension. As we state in our manuscript: "Despite advances in noninvasive imaging technology, cardiac catheterization remains the gold standard for initial diagnosis, choice of initial pharmacotherapy, and longitudinal assessment of patients with PH." We do not agree with the contention that "possible interpretation that children with PH should not undergo cardiac catheterization because of the risks of severe adverse events" from Drs. Hansmann's and Apitz's correspondence or that our manuscript will "cause a drift away from heart catheterization procedures," as suggested by Beghetti et al. We are hopeful that our study leads to continued research and improvements in the safety of catheterization in all children with pulmonary hypertension.

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