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ORIGINAL ARTICLE

Assessing Pulmonary Arterial Hypertension in Infants With Severe Chronic Lung Disease of Infancy: A Role for a Pulmonary Artery Catheter?

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Abstract The treatment of pulmonary arterial hypertension (PAH) associated with chronic lung disease of infancy (CLDI) is becoming commonplace. However, an optimal approach to the monitoring of this treatment has not been clearly established, and data suggest that such therapy may not be without risk. This study assessed the feasibility and safety of pulmonary artery catheter (PAC) placement and its role in the management of PAH associated with CLDI. The medical records of 12 infants with CLDI requiring chronic mechanical ventilation who underwent PAC monitoring were reviewed. Data analyzed included demographics, hemodynamic data, PAH pharmacological therapy, respiratory support, echocardiographic data, sedation level, complications related to PAC use, and mortality. In this analysis, PAC placement and monitoring was found to be feasible, appeared safe, and was associated with the ability to wean inspired oxygen, decrease sedation, and titrate PAH therapy without untoward effect. However, no definitive conclusions can be drawn from this report given its small sample size and uncontrolled, retrospective design. It is hoped that these data will renew interest in PAC monitoring for CLDI and foster prospective study where its true value can be ascertained.

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Introduction

Pulmonary arterial hypertension (PAH) is now considered to be an integral component of the pathophysiology of chronic lung disease of infancy (CLDI) [4, 6, 9]. However, the most appropriate approach to the identification and treatment of PAH in this patient population has not been established. Echocardiography is commonly used; however, its accuracy and precision in assessing PAH has been questioned [5, 12, 14]. Its use is complicated by technician dependence, reliance on indirect methods of determining pulmonary artery (PA) pressures, and frequently, poor echocardiographic "windows" in these children with hyperinflated lung fields. Cardiac catheterization, the "gold standard" in diagnosing PAH, eliminates the imprecision of echocardiography. However, it may not be reflective of the true physiological state of the patient, which is performed under the "ideal" conditions of deep sedation and optimal ventilation and oxygenation. In addition, it represents only a single point in time. The use of pulmonary artery catheter (PAC) monitoring in the pediatric or cardiac intensive care unit allows for the precise monitoring of PA pressures over time and with the patient in a variety of clinical states with different therapies. Given the recent finding that sildenafil treatment of PAH in children was associated with increased mortality in a dose-dependent manner [3], it is clear that the pharmacologic treatment of PAH is not without risk. Therefore, it is imperative that PAH be diagnosed and monitored as effectively as possible. In light of this, we chose to review our

practice of using PAC monitoring to assess PAH in patients with CLDI. We hypothesized that PAC monitoring offers a feasible and safe option to precisely assess PA pressures in these children over time and in a variety of clinical states.

Materials and Methods

The records of all patients admitted to our PICU from 2004 to 2010 with a diagnosis of CLDI requiring mechanical ventilation who had a PAC placed were reviewed. Data abstracted included demographics, weight, sedation level, duration of PAC monitoring, complications associated with PAC use, hemodynamic data, echocardiographic findings, ventilator settings [positive end expiratory pressure and fraction of inspired oxygen (FiO_2)], medications used for PAH treatment, and outcomes. Sedation levels were defined using the Penn State Hershey Children's Hospital sedation algorithm for ventilated children [16]. This validated sedation algorithm assigns a score of 1–6 to identify the desired level of sedation. Higher scores indicate deeper levels of sedation.

Data abstracted specifically pertaining to PAC included the anatomical site of insertion, total duration of PAC monitoring, hourly PA systolic, diastolic and mean pressures, and systemic arterial systolic, diastolic, and mean pressures. All documented PA occlusion pressures were also recorded. The ratio of mean PA pressure to mean systemic arterial pressure was also determined. PAH was defined in the standard manner as mean PA pressure $\geq$25 mmHg by PAC monitoring [2]. For analysis, the initial hemodynamic data were defined as the first recorded values obtained after a brief period of equilibration after catheter placement and procedural sedation. The final hemodynamic data were determined by taking the average of the final 5 h of data before discontinuing the catheter. The decision to average these measurements was made *a priori* to minimize the chance of one spurious final result being recorded. This approach was deemed reasonable because changes in pharmacological therapy were not likely to occur during the time period just before catheter discontinuation. In contrast, only the first value was used for the initial hemodynamic data because changes in pharmacological therapy were likely to occur based on that initial reading.

The echocardiogram performed most closely to, but before, placement of the PAC was reviewed by the study cardiologist. In addition, all echocardiograms performed during PAC monitoring were reviewed by the same study cardiologist, who was blinded to the actual PA pressure values. Specific data assessed during review of these echocardiograms consisted of the following: (1) systolic PA pressure estimate based on the tricuspid regurgitant flow velocity; (2) estimated right-ventricular (RV) systolic pressure; (3) presence of interventricular septal flattening during systole and diastole; (4) presence and direction of atrial-level shunt; and (5) qualitative assessment of RV dilation and/or hypertrophy. Systolic PA pressure was calculated using the modified Bernoulli equation—[(tricuspid regurgitation jet peak velocity)^2 $\times$ 4]—plus an assumed right atrial pressure of 5 mmHg [1]. Based on published literature, 5 mmHg was used as a surrogate for the right atrial pressure in the equation because central venous pressure readings were not consistently available at the time of the echocardiogram [7]. PAH was defined echocardiographically by estimated systolic PA pressure $\geq$40 mmHg or subjectively in the presence of septal flattening or RV dilation/hypertrophy.

For analysis, summary statistics [e.g., medians and interquartile ranges (IQRs) for continuous variables and frequencies and proportions for categorical variables] were prepared for all variables. In addition, comparisons were made between the initial and final hemodynamic data, sedation levels, and FiO_2 using Wilcoxon signed rank test. An alpha value of 0.05 was used to determine statistical significance. Statistical analyses were performed using version 9 of the SAS statistical software program (SAS Institute, Cary, NC). The Institutional Review Board of the Pennsylvania State University College of Medicine approved the protocol and waived the requirement for informed consent.

Results

Twelve patients satisfied entry criteria; all subjects ultimately required long-term outpatient ventilation by way of a tracheostomy tube. A 4 Fr single lumen catheter without a thermal dilution thermistor or central vein proximal port (Edwards Lifesciences Corporation, Irvine, CA) was used in all patients. The median gestational age at birth for the cohort was 25 weeks (IQR 24–26.5). The median patient age at time of PAC placement was 6.3 months (IQR 5.0–7.8), and the median patient weight was 4.45 kg (IQR 3.95–5.50). Eight patients were admitted to the unit electively for evaluation of PAH and/or as a transition to chronic ventilation; the other four were admitted because of acute respiratory illness. The four were not part of the eight. No patient was diagnosed with significant left-to-right intracardiac or extracardiac shunts, connective tissue disease, pulmonary thrombosis/embolism, or congenital heart disease associated with pulmonary hypertension. The median PAC monitoring period was 126 h (IQR 89.5–150). The only documented complication was a single bloodstream infection. In that case, there was a delay between introducer insertion and the attempt at PAC placement. No patient died during the hospitalization. Ten patients (83 %) were still alive at the time of initial manuscript preparation

with a median follow-up of 1,121 days (IQR 702–2125.5). Of the two nonsurvivors, both died acutely months after PAC removal. Both died outside our institution and both were still receiving pharmacological therapy for PAH. One died, at 418 days after PAC placement, seemingly related to an acute airway complication. The other died at day 252 after PAC placement secondary to a gastrointestinal-related process. At the time of writing, six patients (50 %) have been weaned from ventilator support, and five (42 %) are decannulated. Six patients (50 %) have been weaned off PAH medications.

The median initial mean PA pressure was 34 mmHg (IQR 31–40). All patients, including those receiving treatment specifically for PAH ($n = 6$), were considered to have PAH based on their initial mean PA pressure (Table 1). Eight patients were receiving FiO_2 $\geq$0.60. The median mean PA pressure at the time of catheter removal was 30 mmHg (IQR 27.5–31). All patients were receiving pharmacologic therapy aimed toward PAH at the end of PAC monitoring; 9 of the 12 were receiving sildenafil at a median daily dose of 3.9 mg/kg/d (IQR 2.1–8.3) (Table 2).

When comparing the hemodynamic data at the end of PAC monitoring with the initial values, PA systolic pressure decreased in 9 of 12 patients; the median decrease for the entire cohort was 5.5 mmHg (IQR 2–15, $P = 0.02$). Similarly, mean PA pressure decreased in 9 of 12 patients; the median decrease was 4.5 mmHg (IQR 0.5–12, $P = 0.06$). There was no change in systolic or mean systemic arterial pressures during PAC monitoring. In terms of medications, 11 patients experienced some change in therapy during PAC monitoring, i.e., a new or additional PAH medication was administered ($n = 9$), sildenafil was changed to an epoprostenol infusion ($n = 1$) and an epoprostenol infusion dosage was significantly increased ($n = 1$). In addition, the sedation level was decreased (median values of 4 at the time of PAC placement vs. 3 at the time of PAC removal, $P = 0.03$), and FiO_2 was weaned during PAC monitoring [median FiO_2 0.65 (IQR 0.53–0.93) at the time of PAC placement vs. 0.45 (IQR 0.40–0.58) at the time of PAC removal, $P = 0.006$]. The study cardiologist diagnosed PAH in 11 of the 12 patients based on the echocardiogram performed before PAC monitoring using a combination of quantitative and qualitative echocardiographic assessments. In the six patients who had echocardiograms performed during PAC monitoring, the echocardiographic estimate of PA systolic pressure correlated well with ($n = 3$), underestimated ($n = 2$), and overestimated ($n = 1$) the actual PAC measurement.

Discussion

The pharmacological treatment of the PAH associated with CLDI is becoming commonplace. The value of such

Table 1 Hemodynamic data and treatment at time of pulmonary artery catheter placement

Subject no.	Systemic pressure (mean) (mmHg)	PA pressure (mean) (mmHg)	Pressure ratio[a]	PAOP (mmHg)[b]	PAH treatment	Vasoactive infusion	Sedation level	FiO_2
1	126/79 (102)	44/24 (33)	0.32	13	Sildenafil, nitric oxide	Dobutamine, milrinone	5	0.85
2	88/54 (66)	44/28 (34)	0.52	12	Sildenafil	Dobutamine, vasopressin	5	1.00
3	113/63 (81)	50/25 (34)	0.42	13	None	None	4	0.80
4	88/52 (67)	36/26 (32)	0.48	13	Nifedipine	None	3	0.30
5	84/41 (60)	70/37 (51)	0.85	16	None	None	4	1.00
6	76/43 (56)	41/22 (30)	0.53	7	None	None	3	0.60
7	92/55 (70)	79/56 (68)	0.97	13	None	None	4	1.00
8	125/65 (96)	59/33 (46)	0.48	14	Sildenafil	None	2	0.60
9	108/51 (75)	50/22 (34)	0.45	15	None	Dobutamine	3	0.50
10	71/45 (56)	36/22 (28)	0.50	12	Epoprostenol	Milrinone	3	0.70
11	93/60 (77)	42/25 (34)	0.44	14	None	None	4	0.50
12	86/46 (65)	35/18 (27)	0.42	16	Sildenafil	None	4	0.55
Mean	96/55 (73)	49/28 (38)	0.53	13	NA	NA	3.7	0.70
Median	90/53 (68.5)	44/25 (34)	0.48	13	NA	NA	4	0.65

The value in parentheses indicates the mean pressure

NA not applicable

[a] Ratio of mean pulmonary artery pressure to mean systemic arterial pressure

[b] Pulmonary artery occlusion pressure

Table 2 Hemodynamic data and treatments at time of pulmonary artery catheter removal

Subject no.	Systemic pressure (mean) (mmHg)	PA pressure (mean) (mmHg)	Pressure ratio (mmHg)	PAH treatment	Vasoactive infusion	Sedation level	FiO_2	PAC (h)
1	112/66 (88)	36/19 (26)	0.30	Sildenafil, nifedipine	Dobutamine	3	0.45	133
2	77/45 (57)	38/23 (30)	0.53	Epoprostenol	Dobutamine	4	0.60	163
3	110/55 (78)	50/28 (39)	0.50	Sildenafil	None	3	0.60	136
4	104/61 (78)	31/14 (23)	0.29	Sildenafil, epoprostenol	None	3	0.40	149
5	83/45 (64)	39/21 (30)	0.47	Sildenafil, epoprostenol	Dobutamine	4	0.60	265
6	92/55 (73)	36/17 (25)	0.34	Sildenafil	None	3	0.40	151
7	84/52 (65)	41/21 (29)	0.45	Nifedipine	Dobutamine	3	0.35	112
8	101/54 (77)	41/21 (31)	0.40	Sildenafil	None	2	0.53	24
9	90/43 (61)	38/23 (30)	0.49	Sildenafil	Milrinone	3	0.45	96
10	78/43 (60)	36/22 (31)	0.52	Epoprostenol	None	3	0.40	119
11	92/52 (69)	38/22 (30)	0.43	Sildenafil	Milrinone	2	0.40	83
12	96/52 (73)	48/21 (36)	0.49	Sildenafil, amlodipine	None	2	0.55	76
Mean	93/52 (70)	39/21 (30)	0.43	NA	NA	2.9	0.48	125.6
Median	92/52 (71)	38/21 (30)	0.46	NA	NA	3	0.45	126

The value in parentheses indicates the mean pressure

NA not applicable

[a] Ratio of mean pulmonary artery pressure to mean systemic arterial pressure

[b] Pulmonary artery occlusion pressure

therapy, however, has not been well established. Recent data suggest that such therapy may be harmful [3]. It is plausible that more effective monitoring may help discern the value of PAH pharmacologic treatment in CLDI and thus guide management. Although the routine use of PAC monitoring has diminished secondary to adult studies questioning its risk-to-benefit ratio [18], the use of PAC monitoring in CLDI represents a relatively different indication in a very different patient population. Two recent reports support the selective use of PAC monitoring in children [19], particularly with PAH [15]. In the current study, the implementation of PAC monitoring in the PICU setting confirmed the presence and accurately measured the severity of PAH in 12 infants with CLDI. These results suggest that its use is feasible in small children. Its use also appeared relatively safe, and it is conceivable that the security of monitoring PA pressures fostered oxygen and sedation weaning, thereby minimizing toxicity and facilitating transfer home.

However, no definitive conclusions should be drawn from this small, retrospective, uncontrolled study. In addition, the lack of consistency in the timing of the PAC placement relative to PAH treatment further compromises the utility of these findings. In some patients, PAC was used to secure the diagnosis of PAH before treatment, whereas in others it was placed after pulmonary vasodilator therapy had already been initiated to assist with titration of therapy. Furthermore, the inability to determine cardiac output impeded the ability to draw clear conclusions from the data. Therapeutic changes that may have decreased pulmonary vascular resistance with a concomitant increase in cardiac output and pulmonary blood flow, may have resulted in negligible changes in PA pressure. Consequently, beneficial effects of therapy may have been overlooked because they resulted in no change in PA pressure.

Despite these limitations, the results of this study may be valuable. The optimal approach to the treatment and monitoring of the PAH associated with CLDI has not been established. Recent data confirm that PAH therapy has the potential for harm in children [3]. However, those data only included pediatric patients >1 year of age and weighing ≥8 kg. Thus, extrapolating those results to this patient population may not be appropriate. Clearly, data do exist supporting the use of long-term PAH treatment in CLDI [8, 10, 13, 17]. However, reports of the utility of PAH therapy in this patient population highlight the potential for sudden and dramatic clinical change, thus suggesting the need for closer monitoring [8, 17]. The continual assessment of PA pressures with PAC affords the opportunity for such monitoring. The utility of invasive PA pressure monitoring has been shown in the cardiac catheterization laboratory in a study of the effects of long-term sildenafil treatment for PAH in CLDI [13]. Continued PAC monitoring in the PICU may be even more useful by allowing for direct and precise measurements of pulmonary pressures over time and during a variety of patient clinical states. The ability to detect changes in a timely manner may allow for more effective titration of therapy, thus potentially optimizing effect and minimizing morbidity.

In conclusion, the results of this report suggest that the use of PAC monitoring is feasible in these small infants despite contentions to the contrary [11]. Moreover, these findings provide data to support the contention of two recent publications arguing for a role of PAC monitoring in children, particularly in the setting of PAH [15, 19]. Finally, the findings provide support for further prospective study and provide insight into the design of such a trial. Future prospective study using standardized protocols with provisions to measure cardiac output and to perform simultaneous echocardiograms may advance the care of this complex and challenging patient population.

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