

Practice variation in the management of patent ductus arteriosus in extremely low birth weight infants in the United States: Survey results among cardiologists and neonatologists

Shyam Sathanandam MD¹  | Stephanie Whiting RN¹ | Jordan Cunningham BSN, RN¹ |
David Zurakowski PhD² | Leah Apalodimas MSN, APN, CCRN, CPNP¹ |
B. Rush Waller MD¹ | Ranjit Philip MD¹  | Athar M. Qureshi MD³

¹University of Tennessee Health Science Center, LeBonheur Children's Hospital, Memphis, Tennessee

²Department of Biostatistics, Harvard Medical School, Boston, Massachusetts

³The Lillie Frank Abercrombie Section of Cardiology, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas

Correspondence

Shyam Sathanandam, MD, University of Tennessee Health Science Center, LeBonheur Children's Hospital, 848 Adams Avenue, Memphis, TN 38103.
Email: shyam@uthsc.edu

Abstract

Background: Patent ductus arteriosus (PDA) is highly prevalent in extremely low birth weight (ELBW), preterm infants. There are diverse management approaches for the PDA in ELBW infants. The objectives of this research were to identify current PDA management practices among cardiologists and neonatologists in the United States, describe any significant differences in management, and describe areas where practices align.

Methods: A survey of 10 questions based on the management of PDA in ELBW infants was conducted among 100 prominent neonatologists from 74 centers and 103 prominent cardiologists from 75 centers. Among the cardiologists, approximately 50% were interventionists who perform transcatheter PDA closures (TCPC). Fisher's exact test was performed to compare practice variations among neonatologists and cardiologists. A potentially biased audience including a combination of health care providers belonging to cardiology, neonatology, and surgery were also surveyed during the International PDA Symposium. The results of this survey were not included for statistical comparison, due to this audience being potentially influenced by the Symposium.

Results: Statistically significant differences were identified between neonatologists and cardiologists regarding the impact of PDA closure on morbidity and mortality, with 80% cardiologists responding that it does vs 54% of neonatologists ($P < .001$), the need for PDA closure ($P < .001$), and the preferred method of PDA closure if indicated ($P < .001$). There was agreement between neonatologists and cardiologists on symptomatic therapy; however more neonatologists favored watchful waiting over intervention in contrast to more cardiologists favoring intervention over observation (77% vs 95%, $P < .001$). Survey responses also identified a need for further training and research on TCPC.

Conclusion: Neonatologists and cardiologists have notable differences in managing PDA, and continued discussion across cardiology and neonatology has the potential to facilitate more of a consensus on best management practices. Further

investigation is needed to identify outcomes in transcatheter PDA closure, particularly in ELBW infants.

KEY WORDS

ELBW, PDA, practice variation, survey, TCPC

1 | INTRODUCTION

A Patent ductus arteriosus (PDA) is found in 40–60% of extremely low birth weight (ELBW—birth weight < 1 kg), preterm infants.¹ Yet, neither is there a consensus on managing ELBW infants with a PDA,² nor do we know which infant will benefit from treatment.^{2–4} Incidences of necrotizing enterocolitis (NEC), chronic lung disease (CLD), and intraventricular hemorrhage (IVH) are associated with PDA,^{5–7} as pulmonary over circulation occurs and systemic circulation is hypoperfused.^{6,7} Management practices can vary from watchful waiting for closure, medical therapy with Cox inhibitors, surgical ligation,³ and transcatheter PDA closure (TCPC).^{8–11} This article presents some of the considerations which determine the modality and timing of PDA treatment, if any, from a sample of 100 prominent cardiologists and neonatologists in the United States. We aimed to identify practice variations among prominent neonatologists in the United States and also to contrast with cardiologists' opinions.

2 | METHODS

Approval for this study and the survey was obtained from the University of Tennessee institutional review board. The survey consisted of nine questions with multiple responses to choose from. The survey was constructed on Survey Monkey (San Mateo, California) and was sent via group emails. The survey was sent out to several prominent neonatologists and cardiologists in the United States. Both groups received the same survey questions and responses to choose, except, the cardiologists had an additional tenth question. The same survey with 10 questions was also emailed to a group of interventional cardiologists who perform TCPC. The participants had the option to skip responding to a question, if they were unsure of the correct response. The survey was closed when responses were obtained from approximately 100 prominent neonatologist and 100 prominent cardiologists in the United States. Since, the survey to the general cardiologists and the interventional cardiologists were sent out simultaneously, we closed the survey when 50 of each had responded.

The survey was also conducted among the attendees of the First International PDA Symposium held in Memphis, Tennessee on May 18 and 19, 2018. This was performed in the penultimate session of the event. The attendees, approximately 170 in all, included physicians, nurses, and other health care providers belonging to cardiology, neonatology, anesthesia, critical care, pulmonology, cardiac

surgery and industry representatives. This was conducted to determine whether the attendees, several of whom had responded to the emailed survey prior to the conference, had been swayed one way or the other by the discussions during the symposium. The attendees of the PDA Symposium were blinded to the results of the National E-Mail survey.

2.1 | Statistical methods

The individual responses to each survey question were represented as a count and percentage to compare within the group of neonatology respondees and cardiology respondees. Since, there were no significant differences in the responses obtained among general cardiologists and interventional cardiologists, they were grouped as one. Fisher's exact test was performed to compare variations in individual responses for each survey question among neonatologists and cardiologists. Though, the attendees of the International PDA Symposium were surveyed toward the end of all discussions, it was decided to not include these responses for statistical comparison, due to this audience being potentially influenced by the symposium. However, we did summarize these responses and represent in individual tables and figures to visually contrast these outcomes.

3 | RESULTS

There were exactly 100 prominent neonatologists from 74 centers and 103 prominent cardiologists from 75 centers that responded to the email survey. Some had skipped responding to a few questions. The International PDA Symposium had 170 attendees from 78 centers and 6 different countries. Up to 154 attendees responded to the survey questions. The results of the survey are presented in this section. Each question had multiple responses. In this section, we will discuss the response to each individual questions in the survey. The results of each questions are expressed in a tabular format with statistical comparison as well in a graphical format.

Question 1. *At your institute, what best describes the routine clinical practice for medical management of a Large PDA in a premature baby born <28 weeks of gestation? (Table 1 and Figure 1)*

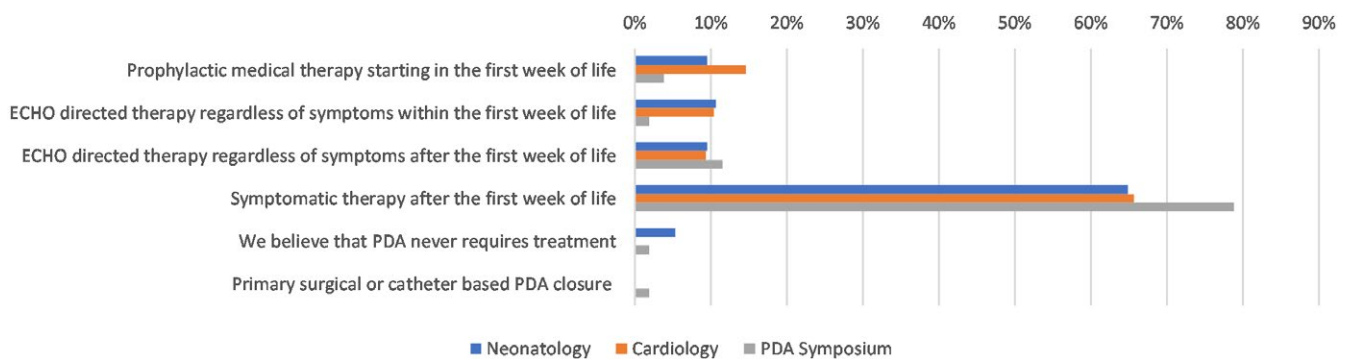
Over 60% of the cardiologists and neonatologists agreed that most hemodynamically significant, large PDAs at this age require at least symptomatic treatment. This was the prevailing sentiment among the attendees of the PDA Symposium as well (79%). At least 5% of the neonatologists responded that they do not believe that

TABLE 1 At your institute, what best describes the routine clinical practice for medical management of a Large PDA in a premature baby born <28 weeks of gestation?

Survey question	Neonatologists N = 94	Cardiologists N = 96	P value	PDA Symposium N = 152
Prophylactic medical therapy starting in the first week of life	10% (n = 9)	15% (n = 14)	.375	4% (n = 6)
ECHO directed therapy regardless of symptoms within the first week of life	11% (n = 10)	10% (n = 10)	1	2% (n = 3)
ECHO directed therapy regardless of symptoms after the first week of life	10% (n = 9)	9% (n = 9)	1	12% (n = 17)
Symptomatic therapy after the first week of life	65% (n = 61)	66% (n = 63)	1	79% (n = 120)
We believe that PDA never requires treatment	5% (n = 5)	0% (n = 0)	.028 ^a	2% (n = 3)
Primary surgical or catheter-based PDA closure	0% (n = 0)	0% (n = 0)	1	2% (n = 3)

^aStatistically significant.

At your institute, what best describes the routine clinical practice for medical management of a Large PDA in a premature baby born <28 weeks of gestation?

**FIGURE 1** Survey results for Question 1

any PDA in the premature infant requires any form treatment, while no cardiologists agreed with this approach ($P = .028$). No one agreed for a primary, prophylactic surgical closure or TCPC.

Question 2. At your institute, how many courses of medical therapy is attempted before referring for either surgical PDA ligation or transcatheter PDA closure? (Table 2 and Figure 2)

Roughly half of the neonatologists responded that they will attempt two courses of medical therapy before referring for an invasive alternative. This was echoed by 55% of the cardiologists and 71% of the conference attendees ($P = NS$). Interestingly, 8% of the neonatologists in the country responded that they would not seek other forms of therapy if medical therapy failed; while, 6% of the neonatologists responded that they would not even attempt medical therapy to close the PDA.

Question 3. At your institute, what is the primary indication for referring a neonate born <28 weeks for surgical PDA ligation or transcatheter PDA closure? (Table 3 and Figure 3)

Though over 70% of the neonatologists and 80% of the cardiologists and conference attendees agreed that the indication for surgical or transcatheter PDA closure is the presence of a large, clinically significant PDA following failed attempts at pharmacological

closure, at least 14% neonatologists vs 1% cardiologists responded that they do not believe any form of therapy including medical therapy is indicated as most PDAs will eventually close ($P < .001$)

Question 4. In your practice center, if medical therapy fails, what is the preferred method of closure of PDA if these resources are available? (Table 4 and Figure 4)

Twenty-three percent of the neonatologists responded that they will not refer for either surgical or transcatheter PDA closure if medical therapy failed vs only 5% of cardiologists who responded that they will forego any further intervention to close the PDA ($P < .001$). Interestingly, all conference goers preferred some form of interventional management. As far as preferred method of closure, 33% of cardiologists preferred TCPC over surgical ligation vs only 13% of the neonatologists preferring TCPC ($P < .001$). Again, interestingly, over 60% of those who attended the conference preferred TCPC over surgery.

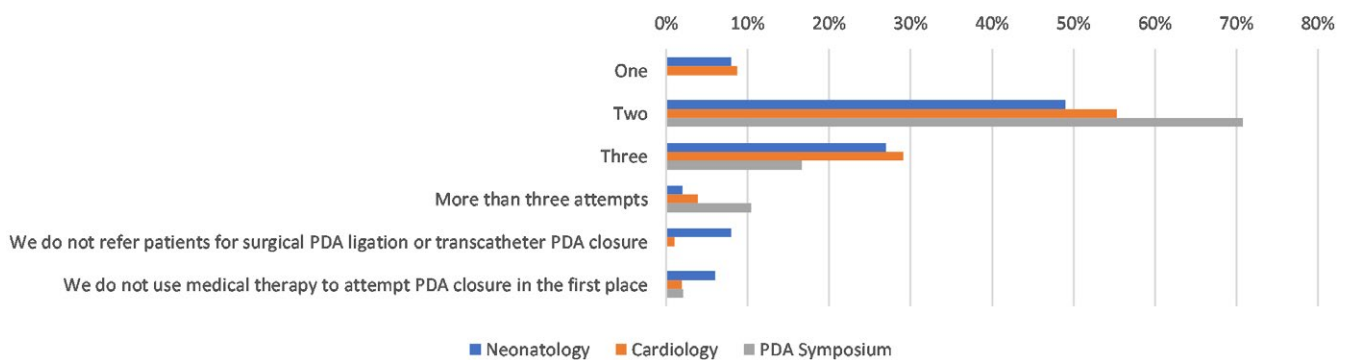
Question 5. At your practice center, with regards to transcatheter PDA closure in premature babies <28 weeks, what are some specific concerns? (Table 5 and Figure 5)

This question allowed the responders to pick more than one response. Thirty-six percent of neonatologists and 16% of cardiologists

TABLE 2 At your institute, how many courses of medical therapy is attempted before referring for either surgical PDA ligation or transcatheter PDA closure?

Survey question	Neonatologists N = 100	Cardiologists N = 103	P value	PDA Symposium N = 148
One	8% (n = 8)	9% (n = 9)	1	0% (n = 0)
Two	49% (n = 49)	55% (n = 57)	.401	71% (n = 105)
Three	27% (n = 27)	29% (n = 30)	.757	17% (n = 25)
More than three attempts	2% (n = 2)	4% (n = 4)	.683	10% (n = 15)
We do not refer patients for surgical PDA ligation or transcatheter PDA closure	8% (n = 8)	1% (n = 1)	.107	0% (n = 0)
We do not use medical therapy to attempt PDA closure in the first place	6% (n = 6)	2% (n = 2)	.166	2% (n = 3)

At your institute, how many courses of medical therapy is attempted before referring for either surgical PDA ligation or transcatheter PDA closure ?

**FIGURE 2** Survey results for Question 2

were unaware that TCPC was feasible in ELBW infants. Interestingly, cardiologists were more concerned than the neonatologists (18% vs 58%, $P < .001$) regarding femoral arterial injury during TCPC, even though this procedure does not entail utilizing the femoral artery for access.

Question 6. At what age do you think the PDA must be closed for best patient outcome in someone born <28 weeks' gestation? (Table 6 and Figure 6)

Thirty-four percent of neonatologists responded that the PDA in this population does not need to be closed. Only 8% of the cardiologists agreed ($P < .001$). At least one-quarter of the cardiologists responded that the PDA must be closed within the first month of life, compared to 10% of the neonatologists ($P = .005$). Almost 50% of the conference attendees agreed that the PDA must be closed within the first month of life.

Question 7. In your opinion, what is the ideal time to perform transcatheter PDA Closure in someone born <28 weeks' gestation? (Table 7 and Figure 7)

Twenty-four percent of the neonatologists felt that TCPC is never needed for these patients. Twenty-five percent of cardiologists felt that the best time to perform TCPC was between weeks 2-4 of life. However, only 11% of the neonatologists agreed ($P = .014$). After attending the conference, 67% agreed that the ideal timing for TCPC in between 2-4 weeks of age.

Question 8. In your opinion what is the lowest weight of a child in whom transcatheter PDA closure can be safely performed? (Table 8 and Figure 8)

Majority of cardiologists (24%) felt that TCPC can be safely performed in children over 1 kg, whereas, the majority of Neonatologists (31%) responded that the ideal weight to perform TCPC would be greater than 2 kg. After attending the symposium, 67% of the attendees were convinced that the procedure can be performed in children weighing between 500-1000 grams.

Question 9. In your opinion and experience, does closing a hemodynamically significant PDA make a difference in morbidity and mortality for children born <28 weeks' gestation? (Table 9 and Figure 9)

As expected, 88% of cardiologists responded that closing the PDA will improve outcomes of ELBW infants compared to only 54% of neonatologists ($P < .001$). Following the conference, 97% of the combined, potentially biased audience agreed that PDA closure will benefit this vulnerable group of children.

Question 10. How many transcatheter PDA closures are performed each year in children <2 kg at your institute? (Table 10 and Figure 10)

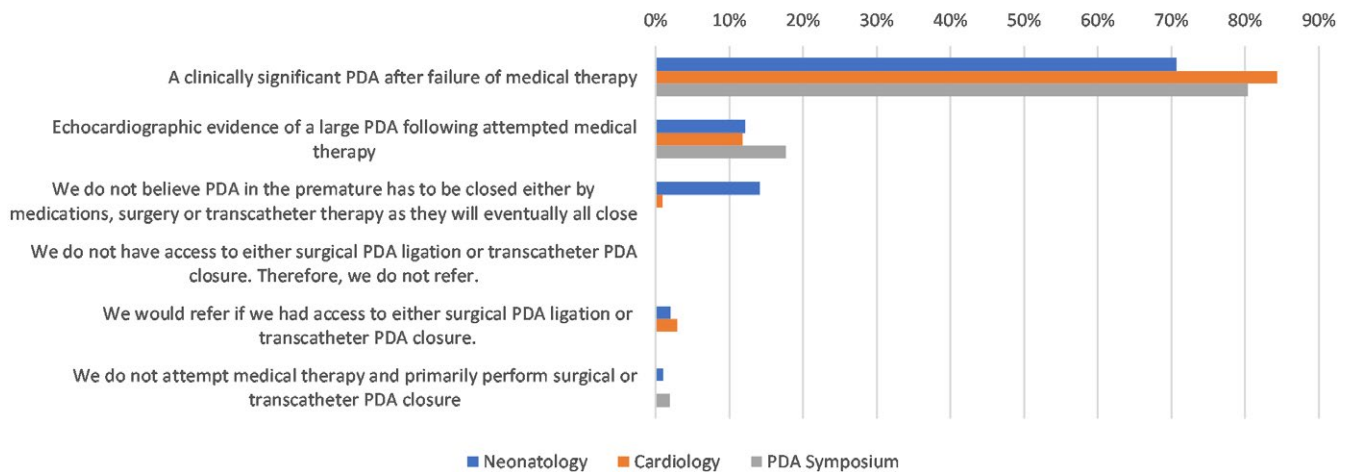
This question was only for the cardiologists. Therefore, no statistical comparisons were performed. Forty-seven percent of the cardiologists responded that they do not perform TCPC in anyone <2 kg. Among those who do close PDAs in children less than 2 kg, 32% perform <5 in a year. Only 5% of the centers perform this procedure

TABLE 3 At your institute, what is the primary indication for referring a neonate born <28 weeks for surgical PDA ligation or transcatheter PDA closure?

Survey question	Neonatologists N = 99	Cardiologists N = 102	P value	PDA Symposium N = 151
A clinically significant PDA after failure of medical therapy	71% (n = 70)	84% (n = 86)	.019 ^a	80% (n = 121)
Echocardiographic evidence of a large PDA following attempted medical therapy	12% (n = 12)	12% (n = 12)	1	18% (n = 27)
We do not believe PDA in the premature has to be closed either by medications, surgery, or transcatheter therapy as they will eventually all close	14% (n = 14)	1% (n = 1)	<.001 ^a	0% (n = 0)
We do not have access to either surgical PDA ligation or transcatheter PDA closure. Therefore, we do not refer	0% (n = 0)	0% (n = 0)	1	0% (n = 0)
We would refer if we had access to either surgical PDA ligation or transcatheter PDA closure	2% (n = 2)	3% (n = 3)	1	0% (n = 0)
We do not attempt medical therapy and primarily perform surgical or transcatheter PDA closure	1% (n = 1)	0% (n = 0)	1	2% (n = 3)

^aStatistically significant.

At your institute, what is the primary indication for referring a neonate born <28 weeks for surgical PDA ligation or transcatheter PDA closure?

**FIGURE 3** Survey results for Question 3

25-50 times a year and only one center performs >50 TCPC in children <2 kg each year.

4 | DISCUSSION

The survey identified areas in which cardiologists and neonatologists agreed, and also pointed out areas where there are significant differences in management of PDA in preterm infants. Some neonatologists (5-14%) responded that even a large, hemodynamically significant PDA in a premature baby never requires treatment including medical management as the majority are likely to close, while no cardiologists agree with this option. Between 24-34% of the neonatologists that attempt pharmacologic closure responded that they would forego surgical or transcatheter closure if the medical therapy failed. Nearly half the neonatologists believe

that closing the PDA does not alter outcomes in children born <28 weeks' gestation, while 88% of the cardiologists disagree with this opinion.

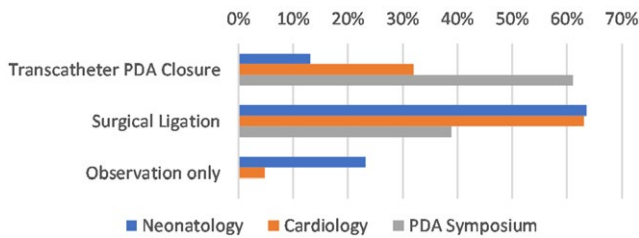
Among those who agreed that they would pursue some form of therapy, there was agreement between cardiologists and neonatologists regarding the number of medical courses attempted before referring the infant for PDA closure, either surgical ligation or (TCPC). Both specialists were in agreement on referring neonates for closure if there was a clinically significant PDA after failed at least two courses of medical therapy. When institutions do believe that closure is needed after failed medical therapy, neonatologists and cardiologists currently prefer surgical ligation (neonatology (64%) and cardiology (63%)) over TCPC (neonatology (13%) and cardiology (32%), $P = .001$), while watchful waiting was selected as the preferred response by 23% of neonatologists and only 5% of cardiologists ($P = .001$, Table 4). Among those who were surveyed, 36%

TABLE 4 In your practice center, if medical therapy fails, what is the preferred method of closure of PDA if these resources are available?

Survey question	Neonatologists N = 99	Cardiologists N = 103	P value	PDA Symposium N = 154
Transcatheter PDA closure	13% (n = 13)	32% (n = 33)	<.001 ^a	61% (n = 94)
Surgical ligation	64% (n = 63)	63% (n = 65)	1	39% (n = 60)
Observation only	23% (n = 23)	5% (n = 5)	<.001 ^a	0% (n = 0)

^aStatistically significant.

In your practice center, if medical therapy fails, what is the preferred method of closure of PDA if these resources are available?

**FIGURE 4** Survey results for Question 4

of neonatologists were unaware that it is feasible to perform TCPC in ELBW infants.

Survey results identified predominant concerns about transcatheter PDA closure, highlighting areas for future training about associated risks, and post-catheterization patient management (Table 5). Many cardiologists and neonatologists are concerned about the technical issues of performing TCPC in extremely small infants. Concerns still include femoral arterial trauma,¹¹⁻¹³ though this vessel is not utilized for access.⁸⁻¹⁰ Other concerns include stenosis of the aorta or the left pulmonary artery and device embolization. There are only minimal concerns regarding exposure to ionizing radiation and contrast agents. Majority of cardiologists felt that TCPC can be safely performed in children over 1 kg, whereas, the majority of neonatologists responded that the ideal

TABLE 5 At your practice center, with regards to transcatheter PDA closure in premature babies <28 weeks, what are some specific concerns?

Survey question	Neonatologists N = 96	Cardiologists N = 98	P value	PDA Symposium N = 143
Trauma to the femoral artery and possible limb ischemia	18% (n = 17)	58% (n = 57)	<.001 ^a	19% (n = 27)
Injury to other vascular structures such as the pulmonary arteries and aorta	18% (n = 17)	43% (n = 42)	<.001 ^a	19% (n = 27)
Device embolization	10% (n = 10)	40% (n = 39)	<.001 ^a	16% (n = 23)
Technical difficulty in performing the procedure in small infants	44% (n = 42)	48% (n = 47)	.568	23% (n = 33)
Not aware of this procedure being an option for small preterm neonates	36% (n = 35)	16% (n = 16)	.002 ^a	9% (n = 13)
Radiation exposure	8% (n = 8)	6% (n = 6)	.591	5% (n = 7)
Injection of contrast agents	6% (n = 6)	7% (n = 7)	1	0% (n = 0)
No concerns	13% (n = 12)	6% (n = 6)	.144	9% (n = 13)

^aStatistically significant.

At your practice center, with regards to transcatheter PDA closure in premature babies <28 weeks, what are some specific concerns?

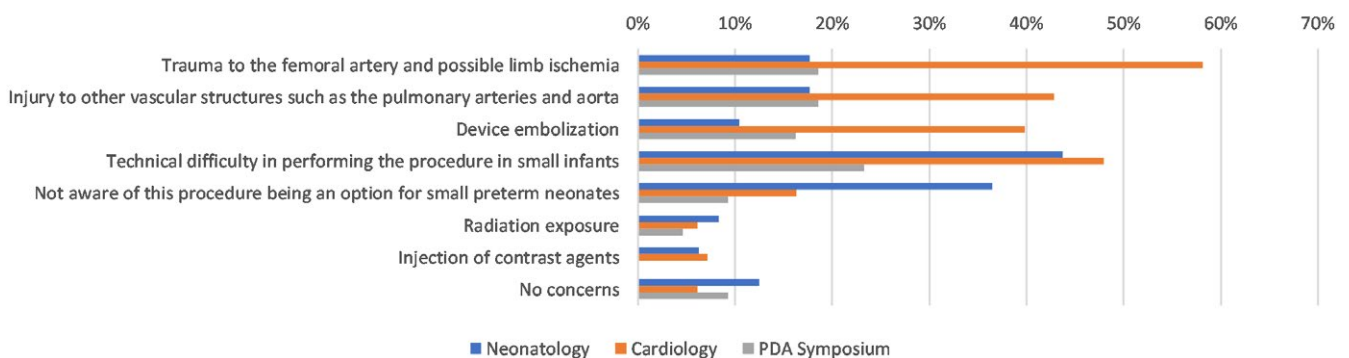
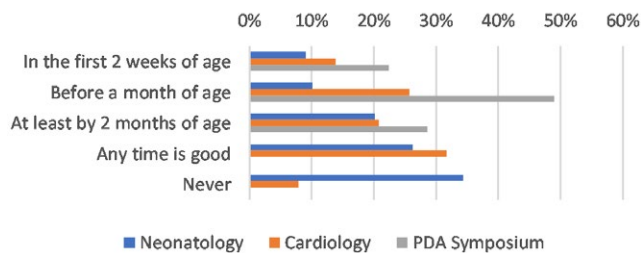
**FIGURE 5** Survey results for Question 5

TABLE 6 At what age do you think the PDA must be closed for best patient outcome in someone born <28 weeks' gestation?

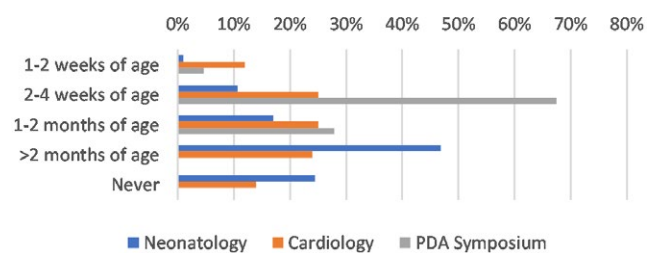
Survey question	Neonatologists N = 99	Cardiologists N = 101	P value	PDA Symposium N = 149
In the first 2 weeks of age	9% (n = 9)	14% (n = 14)	.376	22% (n = 33)
Before a month of age	10% (n = 10)	26% (n = 26)	.005 ^a	49% (n = 73)
At least by 2 months of age	20% (n = 20)	21% (n = 21)	1	29% (n = 43)
Any time is good	26% (n = 26)	32% (n = 32)	.437	0% (n = 0)
Never	34% (n = 34)	8% (n = 8)	<.001 ^a	0% (n = 0)

^aStatistically significant.

At what age do you think the PDA must be closed for best patient outcome in someone born < 28 weeks' gestation?

**FIGURE 6** Survey results for Question 6

In your opinion, what is the ideal time to perform transcatheter PDA Closure in someone born < 28 weeks' gestation?

**FIGURE 7** Survey results for Question 7**TABLE 7** In your opinion, what is the ideal time to perform transcatheter PDA Closure in someone born <28 weeks' gestation?

Survey question	Neonatologists N = 94	Cardiologists N = 100	P value	PDA Symposium N = 143
1-2 weeks of age	1% (n = 1)	12% (n = 12)	.003 ^a	5% (n = 7)
2-4 weeks of age	11% (n = 10)	25% (n = 25)	.014 ^a	67% (n = 96)
1-2 months of age	17% (n = 16)	25% (n = 25)	.218	28% (n = 40)
>2 months of age	47% (n = 44)	24% (n = 24)	<.001 ^a	0% (n = 0)
Never	24% (n = 23)	14% (n = 14)	.071	0% (n = 0)

^aStatistically significant.

weight to perform TCPC would be greater than 2 kg. A fourth of cardiologists felt that the best time to perform TCPC was between weeks 2-4 of life; though only 11% of the neonatologist concurred.

Although statistical analysis was not reported for responses from attendees of the PDA Symposium where both neonatologists and cardiologists were represented, the answers are more unified. The International PDA Symposium was able to change opinions of the attendees. After attending the conference, 67% agreed that the ideal timing for TCPC in between 2-4 weeks of age, 67% of the attendees were convinced that the procedure can be performed in children weighing between 500-1000 grams, and 97% were convinced that closing the PDA will improve outcomes of these critically ill newborns. Continued discussion and education about closing PDA has the potential to facilitate more of a consensus regarding best management practices.

There is ongoing debate on how to manage PDA in preterm infants.^{2,3,14,15} As illustrated in this survey, 50% of the neonatologists

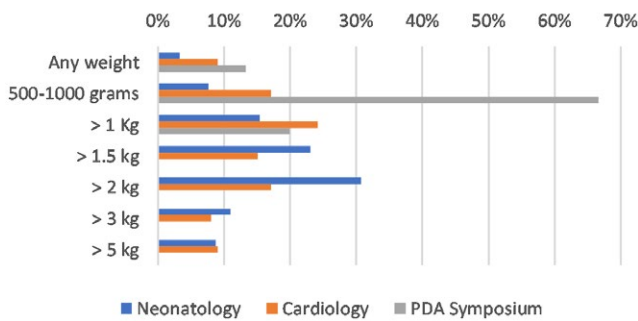
are unsure of potential benefits of PDA closure in ELBW infants. This skepticism could be secondary to the fact that there has been no good treatment options so far. Medical therapy is at best 50% effective in children born 23-26 weeks' gestation¹⁶ and surgical ligation cause unwanted complications secondary to the thoracotomy, conceivably more data are needed about outcomes of TCPC, as it may shift the discussion regarding benefits of closing PDA using this method. TCPC is a relatively new technique that is constantly being refined for the purpose of performing this procedure safely in ELBW infants. Among the many advantages of TCPC over medical therapy is that it guarantees definitive closure of the PDA with limited risks (as low as 3% in some reports in ELBW infants).¹⁷ Since, no "cutting and stitching" of the baby is required unlike surgical ligation, it can prevent complications associated with thoracotomy including post-ligation syndrome.¹⁷ Since this is a new therapy, awareness among neonatologists regarding the feasibility and safety of this technique is still lacking. Events such

TABLE 8 In your opinion what is the lowest weight of a child in whom transcatheter PDA closure can be safely performed?

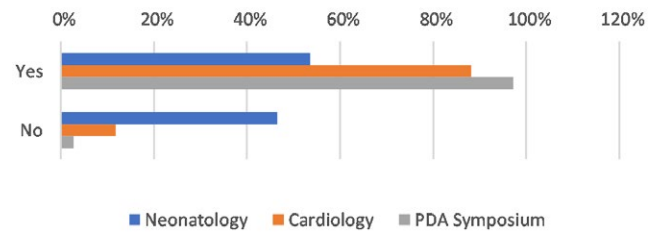
Survey question	Neonatologists N = 91	Cardiologists N = 99	P value	PDA Symposium N = 145
Any weight	3% (n = 3)	9% (n = 9)	.137	13% (n = 19)
500-1000 g	8% (n = 7)	17% (n = 17)	.079	67% (n = 97)
>1 kg	15% (n = 14)	24% (n = 24)	.148	20% (n = 29)
>1.5 kg	23% (n = 21)	15% (n = 15)	.196	0% (n = 0)
>2 kg	31% (n = 28)	17% (n = 17)	.028 ^a	0% (n = 0)
>3 kg	11% (n = 10)	8% (n = 8)	.622	0% (n = 0)
>5 kg	9% (n = 8)	9% (n = 9)	1	0% (n = 0)

^aStatistically significant.

In your opinion what is the lowest weight of a child in whom transcatheter PDA closure can be safely performed?

**FIGURE 8** Survey results for Question 8

In your opinion and experience, does closing a hemodynamically significant PDA make a difference in morbidity and mortality for children born < 28 weeks' gestation?

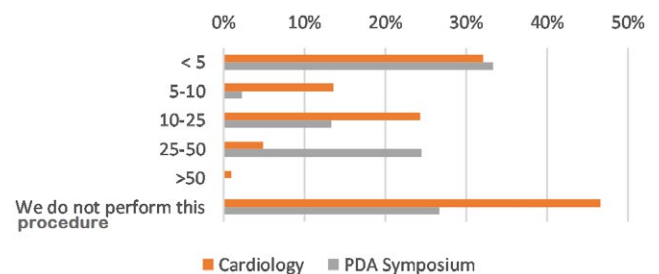
**FIGURE 9** Survey results for Question 9**TABLE 9** In your opinion and experience, does closing a hemodynamically significant PDA make a difference in morbidity and mortality for children born <28 weeks' gestation?

Survey question	Neonatologists N = 99	Cardiologists N = 102	P value	PDA Symposium N = 136
Yes	54% (n = 53)	88% (n = 90)	<.001 ^a	97% (n = 132)
No	46% (n = 46)	12% (n = 12)	<.001 ^a	3% (n = 4)

^aStatistically significant.**TABLE 10** How many transcatheter PDA closures are performed each year in children <2 kg at your institute?

Survey question	Cardiologists N = 103	PDA Symposium N = 145
<5	32% (n = 33)	33% (n = 48)
5-10	14% (n = 14)	2% (n = 3)
10-25	24% (n = 25)	13% (n = 19)
25-50	5% (n = 5)	24% (n = 35)
>50	1% (n = 1)	0% (n = 0)
We do not perform this procedure	47% (n = 48)	27% (n = 40)

How many transcatheter PDA closures are performed each year in children < 2 kg at your institute?

**FIGURE 10** Survey results for Question 10

as the International PDA Symposium could help educate referring specialists. Given the potential benefits of TCPC over more standard therapies for PDA, we suspect that the role of TCPC in ELBW infants will grow steadily. However, the most important question in the mind of most neonatologists is whether the PDA needs to be closed at all as illustrated by the survey results. Perhaps a randomized control trial comparing TCPC vs observation alone could lay this concern to rest. Interventional cardiologists who currently perform or strive to perform TCPC in ELBW infants must maintain equipoise between boldness and commonsense. If proven to be safe and beneficial, TCPC may eventually find its way into the management algorithm of ELBW infants around the world.

5 | CONCLUSIONS

There are immense variations in the practice of managing PDAs in extremely premature infants in the United States. Neonatologists and cardiologists have differing opinions on the consequence of a hemodynamically significant PDA in the eventual outcomes of these infants. The feasibility and safety of TCPC in ELBW infants is still not established. However, TCPC, a new, alternate therapy, has the potential to change management algorithms as evidenced by the influence in survey responses following the First International PDA Symposium.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Study conceptualization, drafting article, critical revision of article, approval of article: Sathanandam, Qureshi.

Drafting article, critical revision of article, approval of article: Whiting, Cunningham, Philip

Statistical analysis, drafting article, critical revision, approval of article: Zurakowski

Critical revision of article, approval of article: Apalodimas, Waller

ORCID

Shyam Sathanandam  <https://orcid.org/0000-0001-8639-0852>

Ranjit Philip  <https://orcid.org/0000-0003-3748-0215>

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