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Does transthoracic echocardiography misjudge the size of patent ductus arteriosus in infants with bronchopulmonary dysplasia?

A. Study Purpose and Rationale

Bronchopulmonary dysplasia (BPD) is a common premature condition that results in significant morbidity and mortality. Its precursor, respiratory distress syndrome, or hyaline membrane disease, results from an insufficient production of surfactant due to lack of lung maturity in the premature infant. The classic definition of BPD was the need for supplemental oxygen or respiratory support at 36 weeks post-gestational age. However, with the advancement in respiratory support and pharmacologic therapy including surfactant, more and more of the extremely premature or very low birth weight neonates are surviving to infancy, which muddies the pure gestational age definition. More recent definitions of BPD require 28 postnatal days of supplemental oxygen or other respiratory support, and include 'mild', 'moderate', and 'severe' categories based on post-gestational age and degree of support. BPD is a disease of premature, low birth weight infants, with babies weighing less than 1250 grams accounting for 97% of BPD cases. (1,2,6)

Patent ductus arteriosus (PDA) refers to the persistence of the ductus arteriosus, a critical fetal vessel connecting the pulmonary and aortic systems that allows fetal blood to bypass the lungs in utero. After the onset of respiration, normal fetal-to-neonatal transition involves the constriction of the ductus arteriosus and its eventual closure, through mechanisms related to increased oxygen saturation, decreased prostaglandins, and changes in pulmonary vascular resistance. PDA results after the failure of the ductus to functionally close within the first 3-5 days of life. PDA is common (30%) in premature and low birth weight infants, and its delay in closure is inversely proportional to a patient's gestational age, occurring via dysregulation of many of the aforementioned processes. The severe sequelae of unrepaired, hemodynamically significant PDAs include left sided overload with subsequent pulmonary edema and pulmonary hypertension, as well as cardiogenic shock. Clinically significant PDAs contribute to pulmonary edema and BPD, and BPD affects PDA hemodynamics. (3,4,5,6,8)

While some PDAs can be observed and can close on their own, hemodynamically and clinically significant PDAs require intervention to prevent the sequelae above. Interventions for PDAs include medical closure with prostaglandin inhibitors, surgical ligation, or, more recently, percutaneous catheter occlusion with coils or other occluding devices (e.g. Amplatzer) under interventional cardiology. (9, 10)

At our academic center, there is anecdotal evidence that echocardiography (echo), the standard diagnostic modality for PDA, may inaccurately assess PDA size. This

has important implications for planned repairs in the cardiac catheterization laboratory, as the pediatric interventional cardiologist prepares to place a well-sized device based on echo estimations of PDA size. If, for example, during the procedure the PDA is significantly larger than anticipated, equipment may need to be substituted – prolonging operative and anesthetic times for these already high-risk patients – or the case may need to be abandoned altogether, with the PDA instead closed via surgical ligation. The potential misjudgment of PDA size is less relevant for planned surgical repair, given that ligation occurs from an extraluminal approach.

It would be helpful to retrospectively assess our center's frequency of misjudgment of PDA size via echocardiography, and, if possible, characterize any clinical features that might predispose a patient to having an inaccurate echo. In addition, these results could suggest possible etiologies for this inaccuracy, e.g. transient right-to-left shunting through the PDA, interatrial shunting, or PDA vasospasm. (12).

B. Study Design and Statistical Analysis

We will perform a retrospective study of infants with BPD and repaired PDA (via interventional cardiology methods of percutaneous coil or occluding device) at Morgan Stanley Children's Hospital of New York Presbyterian. We will investigate how often echocardiography misjudges the size of PDAs, as evidenced by expected size via echo, versus actual size repaired in the catheterization laboratory.

The study will be a retrospective review of medical records, including re-evaluating echocardiographic images (to accurately quantify PDA size, which in the echo reports may only be listed as 'mild', 'moderate', or 'severe'), and investigating operative reports from PDA repairs to evaluate planned versus actual device size. In addition, clinical data will be obtained (related to the time of echocardiography), including gestational age, weight, level of respiratory support, vital signs including pre- and post-ductal oxygen saturations, pulse pressure, and pharmacologic intervention including diuretic therapy. The information collected will have been documented as part of the patient's prior care; no additional procedures or tests will be performed.

The study's primary aim is concerned with how often echocardiograms misjudge PDA size in patients with BPD, and if over- or under-estimation is more common. I estimate that echocardiogram misjudges PDA size 25% of the time, underestimating during the vast majority of misjudged cases.

Using the two groups formed by the primary question (the patients with BPD whose PDA size was accurately predicted by echocardiography [Group A] vs the patients with BPD whose PDA size was inaccurately predicted by echocardiography [Group B]), secondary questions will be studied in a case-control fashion.

Comparing group A and group B, we will investigate the following parameters: 1) level of respiratory support (as proxy of severity of lung disease), 2) pre- and post-ductal saturation difference, 3) pulse pressure, 4) diuretic medications

Predictions:
1) Respiratory support: Room air (RA) + Nasal Cannula (NC) vs continuous positive airway pressure (CPAP) or any mechanical ventilation (SIMV, oscillator, etc.)
I predict patients in Group B will more often have increased respiratory support (by proxy, those with more severe lung disease) than patients in Group A. Assuming Group A (echos accurately predicted PDA size) had increased ventilator support 30% of the time, I estimate group B will have increased support 50% of the time.

Using chi-square test, where Group B is 3 times the size of Group A, and Group A proportion 0.3, Group B proportion 0.5, this will require 207 subjects in Group A and 69 subjects in Group B.

2) Pre- and post-ductal saturation difference.
I predict patients in Group B will have a larger mean pre – post ductal saturation difference, and think a clinically significant difference would be 2% saturation difference.

Using unpaired t-test, assuming standard deviation of 2.5%, this requires 54 subjects in Group A, 18 subjects in Group B.

3) Pulse pressure
I predict patients in Group B will have a larger pulse pressure by a clinically significant 10 mm Hg.

Using unpaired t-test, assuming standard deviation 15 mm Hg, this requires 76 subjects in Group A, 26 subjects in Group B

4) Diuretic medications
I predict patients in Group B will be on diuretic medications 40% of the time, while Group A will be on diuretic medications 20% of the time.

Using chi-square test, this would require 174 subjects in Group A, 58 subjects in Group B.

The greatest numbers are required for parameter 1, thus a total study population of 276 patients would be adequate for all of the questions above. All calculations assume alpha = 0.05, Power 80%.

C. Study Procedure

The study will be a retrospective review of medical records, including echocardiography data, operation reports, and clinical data as above. The information collected will have been documented as part of the patient's prior care; no additional procedures or tests will be performed.

D. Study Drugs

This is a retrospective review of medical records. While one of the study parameters will be medications that patients were taking, no drugs will be administered for the purposes of this study.

E. Medical Devices

There will be no medical devices used in this study, although we are studying patients who have undergone a percutaneous closure of PDA.

F. Study Questionnaires

There will be no questionnaires in this study.

G. Study Subjects

The study population includes all patients at Morgan Stanley Children's Hospital of New York with the diagnosis of bronchopulmonary dysplasia who have had percutaneous closure of the PDA between 2009 and 2014. Patients will be identified based on billing data from the neonatal intensive care unit (NICU) and the division of pediatric cardiology.

Inclusion criteria for this study will include 1) premature birth less than 37 weeks gestational age, 2) bronchopulmonary dysplasia defined as having a requirement for supplemental oxygen for at least 28 days, 3) repair of PDA via percutaneous method (transcatheter coil or device occlusion).

Patients will be excluded from the study if they undergo surgical ligation of the PDA, or if they have any other congenital heart defects.

H. Recruitment of Subjects

This is a retrospective chart review, therefore there will be no active recruitment of subjects. Patients who have undergone transcatheter closure of PDA will be identified, and subsequent clinical information will be obtained from the patients' electronic medical records.

I. Confidentiality and Study Data

All patient data obtained for study purposes will be de-identified by assigning a unique code to each patient. There will be a separate file containing the codes and any identifying information, which will be available only to the study coordinator and primary investigators. All electronic files with patient data will be stored on an encrypted drive that is password protected and is only accessible to study investigators.

J. Potential Conflict of Interest

There are no potential conflicts of interest in this study.

K. Location of the Study

Columbia University Medical Center, Department of Pediatrics

L. Potential Risks

There are no potential risks to subjects as this is a retrospective review of their clinical data.

M. Potential Benefits

There will be no direct benefits for the patients whose data will be used in this study. However, the study may have implications for future patients with BPD and PDA who are undergoing echocardiography.

N. Alternative therapies

This is a retrospective study in which the patients will have already undergone PDA closure.

O. Compensation to Subjects

This is a retrospective analysis, thus there will be no compensation for the subjects.

P. Costs to Subjects

This is a retrospective analysis, thus there will be no cost to the subjects.

Q. Minors as Research Subjects

This study is a retrospective observational study involving data obtained from the medical records of minors. Approval from the Department of Pediatrics Committee on Human Investigation will be obtained prior to the initiation of the study.

R. Radiation or Radioactive Substances

No radiation or radioactive substances will be used in this study.

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