January 2011

Partial Exchange Transfusion For Polycythemia Hyperviscosity Syndrome

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Partial Exchange Transfusion for Polycythemia Hyperviscosity Syndrome

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

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2011

Abstract

PARTIAL EXCHANGE TRANSFUSION FOR POLYCYTHEMIA HYPERVISCOSITY SYNDROME: A 21-YEAR REVIEW Bridget L. Hopewell, Laurie A. Steiner, Richard A. Ehrenkranz, Matthew J. Bizzarro, and Patrick G. Gallagher. Division of Perinatal Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The objective of this study was to examine the use of partial exchange transfusion (PET) performed for polycythemia hyperviscosity syndrome (PHS) over time. A retrospective review of 141 infants who received a PET for PHS at Yale-New Haven Hospital, between 1986-2007 was performed, querying maternal and neonatal medical records. Patient demographics, risk factors for PHS, indications for PET, and complications associated with PET and PHS were collected. Overall, there was no change in the number of PET performed over the study period ($r^2=0.082$, $p=0.192$). Eighty-eight percent of patients had at least one risk factor for PHS, most commonly maternal diabetes. Over time, there was a statistically significant decrease in maternal diabetes as a risk factor for PHS. Forty percent of patients had a significant complication attributed to PHS prior to PET. Eighteen percent of patients had a complication attributed to PET. Life-threatening complications of PHS or PET were rare. In conclusion, PHS continues to be a problem observed in neonatal intensive care units, particularly in at-risk populations. PHS and PET are associated with significant complications. Well designed studies with long-term follow up are needed to assess the risks and benefits of PET for PHS.

Acknowledgements

I would like to acknowledge my thesis advisor and mentor, Dr. Patrick Gallagher.

I would like to acknowledge my co-authors, Laurie Steiner, Matthew Bizzarro, and Richard Ehrenkranz.

I would like to acknowledge Howard Pearson, the pediatric department thesis chair.

I would like to acknowledge the Office of Student Research at Yale University School of Medicine.

Supported in part by T32 HD07094 (LAS)

Supported in part by the Yale School of Medicine Summer Research Stipend

An abbreviated version of this paper with the same title and authorship was accepted for publication to the American Journal of Perinatology on January 5, 2011.

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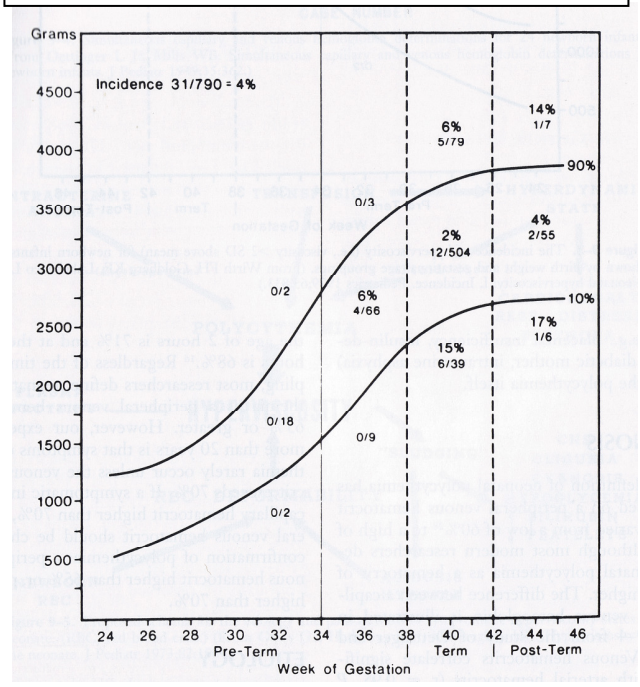
Introduction

Neonatal polycythemia, a condition in which the percentage of whole blood occupied by red blood cells is increased, is a diagnosis recognized since antiquity. The first case is thought to be a *red* first-born twin recorded in the Bible (Genesis 25:25). Though the condition has been known and recognized, interest has waxed and waned over the past few decades. There was a flurry of research during the 1970s and 1980s in which animal models were developed, some randomized trials were undertaken, diagnostic tools were developed and debated, and meetings abounded with controversy over both the diagnosis and treatment. However, even though polycythemia is still a common problem, occurring in 1-5.4% of live births,[1-6] the literature has remained largely silent for the past 25 years, leaving many of the controversial questions unexplored.

***Figure 1**: Incidence of venous polycythemia (hct >/= 65%) by birth weight and gestational age groupings.[1]*



Because our clinical observations indicate that polycythemia continues to be a common diagnosis and both the condition and its treatment carry significant risks of morbidity, we felt it was time to re-explore this condition. Our first step in re-opening this topic for close examination was to determine how the research from

the 1970s and 1980s affected the clinical practice here at Yale-New Haven Hospital. In addition, we wanted to further define the population affected and delineate their risks for morbidity.

Definitions

Polycythemia and Hyperviscosity are often used interchangeably though they are not equivalent. Neonatal Polycythemia is significant only because it can lead to Hyperviscosity syndrome which can lead to alterations in blood flow, sludging of blood in vessels, clotting or ischemia, leading to end organ damage. An increased concentration of red blood cells can lead to increased blood viscosity, but this is also affected by plasma proteins, red cell deformability, hypoxia, and acidosis. The resulting associated constellation of clinical and laboratory findings is called polycythemia hyperviscosity syndrome (PHS).[7]

Fetal Erythropoiesis

Fetal erythropoiesis first begins in the yolk sac until the third to the sixth month when the liver takes over as the main source of erythropoiesis. Bone marrow, the major site of adult erythropoiesis, becomes important during the last 3 months of gestation.

The most well-known difference between fetal erythrocytes and adult red blood cells (RBCs) is that the hemoglobin in fetal erythrocytes has a higher oxygen affinity which aids in transfer of oxygen from maternal to fetal RBCs. In addition, they also differ in their membrane proteins, surface antigens, and metabolic enzyme patterns. They also have a larger mean cell volume and mean cell hematocrit as compared to adult RBCs. [8]

The fetus adapts to the relatively hypoxic intrauterine environment by increased erythropoiesis.[9] As such, the red blood cell mass of a newborn infant compared to later infancy, childhood, and adulthood, is significantly increased. However, this physiologic increase in red blood cell mass can be pathologically increased by either primary (increased fetal erythropoietic activity) or secondary (transfusion of RBCs) causes, or reduced plasma volume, leading to polycythemia.[10]

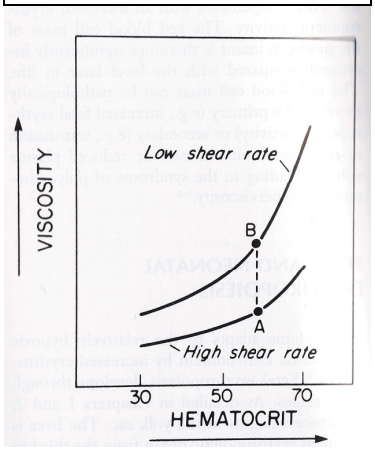
Blood Viscosity

Viscosity of a newtonian fluid was described by Poiseuille as the ratio of shear stress to shear rate as such:[11]

$$\text{Viscosity} = \frac{\text{shear stress}}{\text{shear rate}} = \frac{(p-p^1)r^4\pi}{8lQ}$$

where $p-p^1$ is the pressure gradient along the blood vessel, r is the radius, l is the length of the blood vessel and Q is the blood flow. **Figure 2** shows the relationship of viscosity to hematocrit at high and low shear rates. [12]

***Figure 2**: Hematocrit vs. viscosity*



However, blood is not a fully Newtonian fluid as it is a suspension of particles. The viscosity of blood does not remain constant. It varies with the amount of constituents, properties of those constituents, as well as features of the microenvironment of the circulation. Reliable viscometers are in development but are not currently in use clinical use. [13]

Plasma proteins can contribute to the viscosity of whole blood. Adult hyperviscosity syndromes can sometimes be attributed to hyperproteinemia states like diabetes and Waldenstrom's macroglobulinemia.[14,15] However, these are not conditions observed in the newborn. Increasing fibrinogen in plasma also correlates to an increase in viscosity.[16] As such, the viscosity of plasma in the newborn is relatively constant at 1.0 to 1.5 centipose which is very near the viscosity of water, a Newtonian fluid.[16,17] Linderkamp's group saw in their analysis an overall decrease in plasma viscosity leading to decreased whole-blood viscosity in pre-term infants. This led them to consider whether polycythemia was less dangerous in pre-term infants or whether pre-term infants required even lower viscosity to maintain adequate circulation. [16]

The deformability of the RBCs influence viscosity. RBCs in a neonate have been shown to be more deformable than in an adult, but are also more variable in shape which leads to a heterogeneous population of RBCs with respect to their membrane deformability. [18] Aging RBC's are less deformable than young RBC's and this difference in deformability is exaggerated in neonates as compared to adults. [19]

The deformability of leukocytes (WBCs) also can influence whole blood viscosity. Stimulated neutrophils are less deformable than resting neutrophils. [20,21] Inflexible platelets might be suspected to contribute to viscosity. Mean platelet volume has been shown to correlate with plasma viscosity in cardiac patients. [22]

Acidic pH (<7.00) increases blood viscosity.[23] This may be due to fluid shifts into RBCs with decreasing pH. It is hypothesized that along with increasing blood

volume, asphyxia-induced placental transfusion also decreases pH which compounds the increase in viscosity. [24]

The apparent viscosity of whole blood also varies with the size of the vessels. Blood flow is high in large vessels and the apparent viscosity is low, while in small blood vessels the apparent viscosity is high. Changes in the hematocrit cause the greatest changes in viscosity in small blood vessels. However, it has been known since the 1930s that viscosity decreases with decreasing size of the capillary[25] down to 3µm.[26] This represents high hemodynamic efficiency. The hct of blood does not affect the viscosity in the capillary which means that in vitro measurements of blood viscosity may not reflect the viscosity of the blood in the capillary.[24] It has been suggested that viscosity may increase again as the capillary size decreases below 4 mm. The variation in capillary size in different organs may explain the difference in effects of PHS on different organs.[17] In addition, capillary and venous hemoglobin determinations are often quite discordant which hinders clinical decision making.

***Figure 3**: Comparison of capillary and venous hemoglobin in 24 infants*

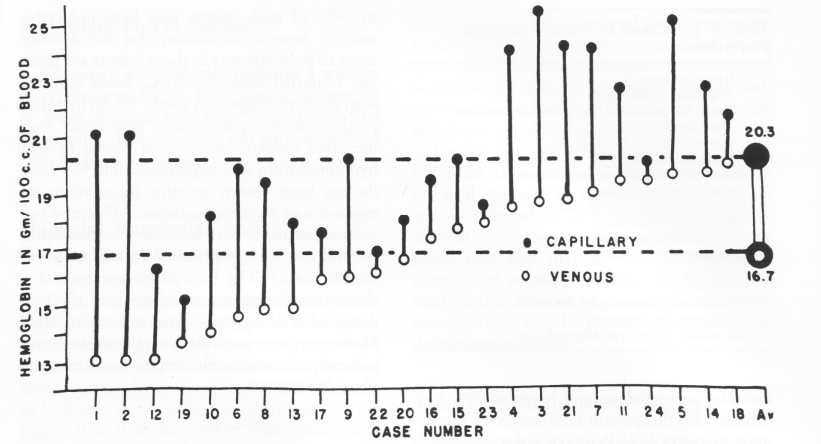


Figure 3 shows simultaneous capillary and venous hemoglobin determinations for 24 newborn infants.[27]

As blood viscosity is not easily or reliably measured clinically, the hematocrit is used as an imperfect measure of PHS and is used with clinical impression to decide on whether or not the child requires treatment. Data has been difficult to interpret because of variation in studies including source of the blood sample and age of the infant at the time of measurement.

Oh and Lind also showed in the 1960's that capillary hematocrit was consistently 10% higher than simultaneously obtained peripheral venous samples.[28] Ramamurthy showed that 80% of infants with an umbilical vein hct >/= 63% have viscosity greater than three standard deviations above the mean and 94% of neonates with an umbilical vein hct <63% had viscosity in the normal range. However, capillary hct, which is usually the first measured in an infant had no significant correlation between peripheral vein hct or umbilical vein hct. [2] The ideal measurement would be the in vivo viscosity of blood in arterioles, venules, and capillaries of key organs,[2] but as this is not accessible, we strive for something that will best correlate. Commonly, a hematocrit of 65% or greater has been used to define polycythemia.

The timing of the blood sample of the hct is important and can influence diagnosis because from birth to 6-12 hours of age, shifts in body water increase the hct, and then decrease the hct similar to the value at birth by about 24 hours. [2,29]

Hemodynamics

Signs and symptoms of PHS are believed to be from disturbances in blood flow in different organs, and thus the hemodynamics have been examined in order to explain the difference in the effects of PHS on different organ systems. There has

been no comprehensive study done on the hemodynamics of PHS and much is still unclear.

With regards to the cardiovascular system, it has been observed in dog models that there is a decrease in cardiac output with relatively little change in oxygen transport or delivery. It has also been shown to increase pulmonary resistance and slightly increase systemic resistance, as well as decrease myocardial blood flow.[30,31] These results have been substantiated in infants as well and the decreased cardiac output appears to be mostly a result of reduction of heart rate with possible reduction in stroke volume. [32,33] Fouron and Herbert used a lamb model to show that pulmonary resistance increases more than systemic resistance. They then showed that with a hct above 70%, the pulmonary and systemic resistance were the same. This also reversed the direction of blood flow through the patent ductus arteriosus. [34]

Boehm et. al found that with increasing hematocrit, bile acid concentration in serum increased and trypsin and lipase activity in duodenal juice was decreased. These findings were greatest in the asymptomatic infants not treated with PET vs. symptomatic infants that were treated. [35] The authors warn that managing these infants nutritionally could be more difficult.

Renal hemodynamics have been examined. In hypervolemic polycythemia caused by delayed cord clamping, it was shown that there was higher renal blood flow, greater GFR and greater urine output.[36] However, in a puppy model of normovolemic polycythemia, it was found that while renal blood flow was preserved, renal plasma flow decreased by 63% and Glomerular Filtration Rate

(GFR) decreased by 53% resulting in significantly decreased urine output as well as electrolyte excretion. [36] It has been hypothesized that the difference between these studies is that both volume status and hct affect renal hemodynamics. [24] Another study showed infants with PHS had decreased GFR, urine output, and sodium excretion which was ameliorated by PET. [37]

Whether peripheral circulation in the feet of infants with PHS is affected is not clear. Some studies show no effect on peripheral circulation,[38] while others show that at a given blood volume, an increase in viscosity decreases peripheral circulation.[39] One study showed a decrease in peripheral blood flow which normalized with PET. However, the infants were neither hypoxic nor hypercarbic before or after the exchange.[40]

Doppler studies of cerebral circulation have shown that polycythemic infants have a significant reduction in cerebral blood flow velocity compared with similar term infants with normal hematocrits and blood viscosity values. The velocity of the blood flow also improved after PET in this study. [41] In a newborn lamb model with induced polycythemia, the same group demonstrated that in polycythemic lambs, the arterial oxygen content was increased. When the arterial oxygen content was reduced but the lamb remained polycythemic, the cerebral blood flow increased to baseline values. This led them to suggest that the reduced flow observed may be caused by an increased oxygen content, rather than increased viscosity.[42] Limitations of most animal models are that polycythemia is induced after birth, rather than as a result of a hostile uterine environment.

Symptoms

Symptoms of polycythemia-hyperviscosity are often nonspecific. Many of the symptoms of PHS can also be attributed to other perinatal problems such as asphyxia or chronic hypoxia and may not be directly caused by PHS. The presence of symptoms makes the diagnosis more likely, but the absence of symptoms does not preclude the diagnosis. These symptoms include a ruddy complexion, lethargy, hypoglycemia, feeding difficulties, hyperbilirubinemia, thrombocytopenia, respiratory distress, cyanosis and seizures. Often the infants have a reddish-blue "ruddy" color in spite of a normal PaO2. Major ischemic clotting events resulting in gangrenous necrosis have also been reported, and were detected antenatally and thus are resistant to treatment.[43] The respiratory distress is hypothesized to be due to the elevated pulmonary vascular resistance and perhaps increased shunting in the lungs.

In addition to poor feeding and vomiting which has been reported with PHS, necrotizing enterocolitis (NEC) has been associated with PHS in several studies.[44,45] However, in a population of patients admitted to a newborn special care unit already at increased risk for developing NEC, it is nearly impossible to attribute the development of NEC specifically to PHS. Necrotizing enterocolitis could be hypothesized to be caused by either sludging of blood in vessels from PHS, disruption of flow from a partial exchange transfusion, or be unrelated due to significant other risk factors in this patient population. One study in an animal model showed the incidence of NEC in polycythemic puppies was 58%.[46] However, Black et al[47] found that NEC occurred with higher frequency in patients who had

received an exchange transfusion, and furthermore found that one third of the infants had pneumatosis intestinalis. Therefore, they argue NEC is caused by the exchange transfusion rather than hyperviscosity. Large, prospective, randomized trials are needed to sort out these relative risks of NEC.

Though renal hemodynamics do seem to be affected, acute renal failure is not seen frequently in infants with PHS, but it has been reported.[48] As with necrotizing enterocolitis, acute renal failure may be multifactorial in origin and whether PHS is contributory or a confounding variable in cases of asphyxia or other risk factors has yet to be sorted out.

Hypoglycemia is a common symptom in polycythemia. Rosenkrantz, using his lamb model, has hypothesized it is due to a reduced plasma volume. [49] Since glucose is carried in the plasma, as plasma is reduced, so is glucose. Furthermore, as blood flow is decreased, the extraction of glucose is increased compounding the problem. Others have suggested that it is due to decreased glucose production resulting from hyperviscosity, though the mechanism is unclear. [50] Another hypothesis is that the excess of red blood cells causes excess glycolysis and increased consumption of glucose by the red blood cells themselves.

Thrombocytopenia, fibrin monomers, and evidence of intravascular thromboplastic activity have been found in infants with PHS.[51] One study found thrombocytopenia in 20% of infants with PHS, but they all had normal coagulation findings.[6] Mechanisms have not been determined, but a clotting risk is hypothesized because of normally low antithrombin III levels combined with impairment of the microcirculation.[52] However, low antithrombin levels are also seen in infants who

have been asphyxiated and it is unknown whether PHS is a confounding variable or an independent risk factor.

In some studies, polycythemic infants have been reported to have worse developmental and neurologic outcomes than their non-polycythemic counterparts. In 1982, Black et al reported 38% incidence of motor and neurologic abnormalities in the infants with PHS compared to 11% of matched controls. [53] Asymptomatic infants with polycythemia have been shown to have increased pulmonary resistance and relative bradycardia which normalized after PET with no change in stroke volume thereby increasing cardiac output in those infants. [33] In his review, Rosenkrantz[24] summarized the frequency of symptoms in 4 major studies as follows:

Table 1: Frequency of Clinical Symptoms Observed in Association with Polycythemia Investigation

Clinical Symptoms	Gross et al[54] (n=18) (%)	Ramamurthy and Brans[2] (n=54) (%)	Black et al[53] (n=111) (%)	Goldberg et al[55] (n=20) (%)
Cyanosis	89	17	7	Nr
Plethora	83	63	Nr	Nr
Tremulous/jittery	67	13	Nr	Nr
Abnormal EEG	33	Nr	Nr	Nr
Seizures	28	0	0	Nr
Respiratory distress	44	4	10	15
Cardiomegaly	17	Nr	Nr	85
Lethargy/poor feeding	Nr	50	+	55
Hyperbilirubinemia	50	6	Nr	5
Abnormal blood smear	50	Nr	Nr	Nr
Thrombocytopenia	39	Nr	Nr	25
Hypoglycemia	33	Nr	27	40
Hypocalcemia	6	Nr	Nr	0

Nr- not reported or examined
+ - greater incidence compared with the control group

Other reported clinical symptoms include irritability, hypotonia, easily startled, vomiting, hepatomegaly, and jaundice.

Pathogenesis

Many perinatal factors are associated with the development of polycythemia including conditions of intrauterine transfusion including twin-twin transfusion, maternal-fetal transfusion, and delayed cord clamping; conditions associated with increased fetal erythropoiesis such as acute and chronic fetal hypoxia, fetal trisomy,

and endocrine abnormalities.[24,56,57] In a large series of infants of diabetic mothers, 5% developed polycythemia.[58] Causes of primary and secondary neonatal polycythemia are summarized in **Table 2**.[59]

Table 2: Causes of primary and secondary neonatal polycythemia

Causes of Primary Neonatal Polycythemia	Causes of Secondary Neonatal Polycythemia
Intrauterine hypoxia **Placental insufficiency** **Small for gestational age, growth retardation** **Preeclampsia** **Severe maternal heart disease** **Maternal smoking**	**Delayed cord clamping**
Maternal insulin-dependent diabetes	**Twin-to-Twin transfusion**
Neonatal thyrotoxicosis	**Maternal-fetal transfusion**
Congenital adrenal hyperplasia	**Dehydration**
High-altitude conditions	**Perinatal asphyxia**
Chromosome abnormalities **Trisomy 13** **Trisomy 18** **Trisomy 21** **Hyperplastic viceromegaly (Beckwith-Wiedemann syndrome)**	
Decreased erythrocyte deformability	

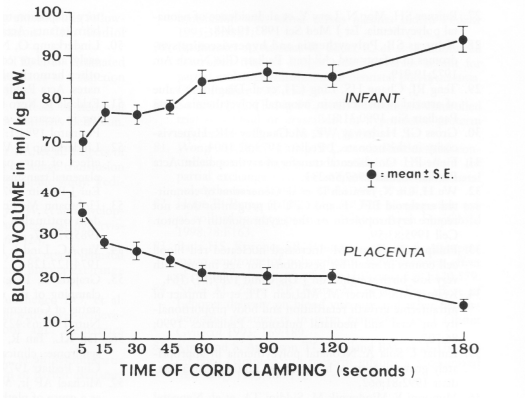
Fetal hypoxia is thought to contribute to polycythemia in two ways. First, it can shift blood from the placental circulation to the fetus, resulting in an increase of both red cell mass and blood volume. Second, hypoxia may contribute to an

increase in fetal production of erythropoietin which stimulates development of more red cells by the fetus. Examples of causes of chronic fetal hypoxia include maternal diabetes, intrauterine growth restriction (IUGR) or small for gestational age fetus (SGA), preeclampsia, placental insufficiency, neonatal thyrotoxicosis, maternal smoking, increased fetal metabolism, and living at high altitude.

Smoking is thought to contribute to the development of PHS because of hypoxia resulting from a nicotine-induced reduction in uteroplacental blood flow as well as an increasing fetal carboxy-hemoglobin. Hypoxia then is thought to increase erythropoietin production. In addition, maternal smoking has been shown to decrease erythrocyte deformability. [60] Awonusonu et al. determined that term neonates of mothers who smoke during pregnancy require PET approximately two and a half times as often as term neonates of mothers who do not smoke. [60]

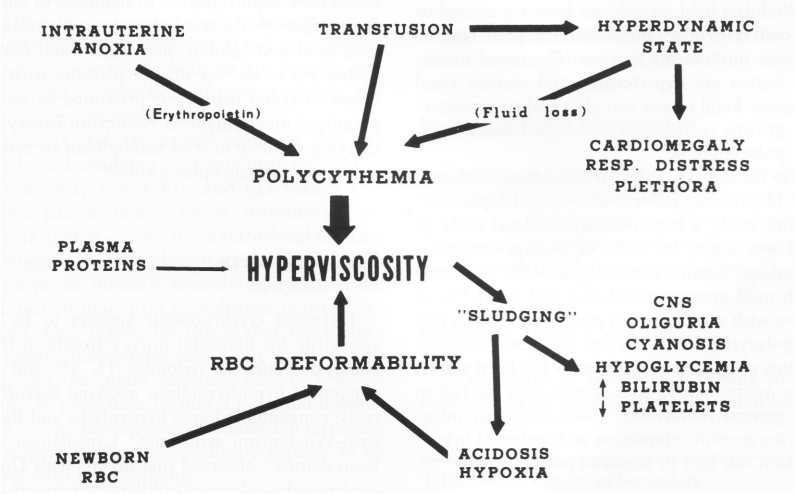
Conditions associated with erythrocyte transfusion such as twin-twin transfusion, maternal-fetal transfusion, and delayed cord clamping are also associated with PHS.[61,62] The relationship between an infants blood volume and placental residual blood volume at various times of cord clamping has been known since 1969 as shown in **Figure 4**.[61] One study showed 14% of infants delivered outside the hospital developed polycythemia.[63]

***Figure 4**: Infant and placental blood volume vs. time of cord clamping.*



In addition, high altitude is associated with a higher incidence of polycythemia, presumably owing to the decreased partial pressure of oxygen. It has been shown that the incidence of polycythemia in Denver, CO at 1610m above sea level was twice that at sea level in Virginia. [1,3] **Figure 5** shows a proposed schema for the etiology and pathogenesis of symptomatic hyperviscosity states in the neonate (RBC, red blood cells).[54]

***Figure 5**: Proposed schematic representation of the etiology and pathogenesis of hyperviscosity in the neonate*



Complications

Table 3: Complications associated with neonatal Polycythemia

Complications Associated with Neonatal Polycythemia
Respiratory distress syndrome
Congestive heart failure
Convulsions
Peripheral gangrene
Priapism
Necrotizing enterocolitis
Ileus
Acute renal failure
Abnormal electroencephalographic pattern

Treatment

To improve clinical symptoms and potentially improve neurologic outcome, isovolemic hemodilution, often called partial exchange transfusion (PET) has been used to reduce the hematocrit. A hematocrit of 60% is the goal of most PET. The blood volume is calculated by this formula:

$$\frac{\text{(Observed hematocrit – Desired hematocrit [60\%])}}{\text{Observed Hematocrit}}$$

The blood volume in the newborn infant is estimated at 80-100 mL/kg body weight. The usual process consists of attaching an empty syringe to the umbilical vein catheter and 5-20mL aliquots are withdrawn. Then, another syringe with saline, Ringer's Lactate, or plasma is infused at the same time or just after. After each aliquot, a rest period of 5-10 minutes is taken in which the infant's vital signs and clinical symptoms are monitored for any complications. The last aliquot drawn is usually sent for a CBC. No studies have shown an advantage for either fresh frozen plasma, albumin, or crystalloid solutions, however with the risk of infection from plasma, most physicians opt for crystalloid solutions, though it requires monitoring of electrolyte status.

The rationale for PET is that reducing presumed hyperviscosity decreases vascular resistance, improves perfusion, and limits end organ damage, thereby preventing or ameliorating complications of PHS.[32,41,64,65] PET may lead to improvement in symptomatology, such as cyanosis, hypoglycemia, thrombocytopenia, and cardiac function in the short term.[6,33,66-68] PET has also been shown to increase skin capillary blood flow velocity in vivo especially when

performed shortly after birth, which is hypothesized to be reflective of other internal organ capillary blood flow.[65] Interestingly, in the study of cerebral blood flow velocity which found the flow velocity was slower in infants with PHS than in nonpolycythemic infants, the polycythemic infants showed an increase in blood flow velocity and a reduction in vascular resistance after being treated with PET.[41] However, even with this evidence of immediate improvement, PET has not been shown to improve long term developmental outcomes in infants with PHS.[66,67,69,70] One study showed that for the first two weeks of life, infants treated with PET for PHS were less irritable, more alert and more easily consoled, but neonatal problems were not predictive of neurologic outcome at 8 months.[55] In addition, one prospective randomized trial in 1985 showed an increase in abdominal distension and bloody emesis and bloody stools in hyperviscous patients receiving PET compared to hyperviscous patients receiving only symptomatic care.[47] The lack of improvement in long term neurologic outcomes has caused many to question the utility of this procedure [71] in light of possible complications that have not been fully defined.

Alternative treatments undertaken include watchful waiting, or increased fluid intake delivered enterally usually by gavage feeding, or parenterally.

The American Academy of Pediatrics guidelines for PET in treatment of PHS are vague: “The accepted treatment of polycythemia is PET. However, there is no evidence that exchange transfusion affects long-term outcome.[72] In the past 20 years, there have been no studies in the English literature assessing the frequency with which PET for PHS is performed, the patient population undergoing PET, the

indications used for initiating PET, and the risks associated with PET. Based on our longitudinal clinical observations, we hypothesized the following: PHS remains a common condition in neonatal intensive care units; PET continues to be used in the treatment of PHS; and both PHS and PET may be associated with neonatal morbidity. To address these hypotheses, we examined the frequency, indications, and complications of PET performed for PHS over the past 22 years at a single institution.

We hope that our study will spur interest in designing controlled studies that will be more helpful in defining which infants will benefit from PET for PHS. We also hope it will remind physicians that even procedures that have been done frequently have risks and help them weigh risks and benefits in their clinical decision making.

Hypotheses

Based on review of the literature and the authors' experience in the Yale-New Haven Children's Hospital Newborn Special Care Unit, we hypothesize that PHS remains a common condition in neonatal intensive care units. We also hypothesize that PET continues to be used in the treatment of PHS. We further hypothesize that both PHS and PET may be associated with neonatal morbidity.

Specific Aims

To address our hypotheses, we have developed these specific aims:

1. Determine frequency of PET for PHS over 21 years at a single institution
2. Evaluate demographic information of patients receiving PET
3. Examine risk factors for developing PHS which necessitates PET
4. Compare recorded indications for PET with recommended indications
5. Examine complications attributable to PHS and/or PET

Patients and Methods

Infants who were long-term admissions (>24 hours) to the Newborn Special Care Unit (NBSCU) at Yale New Haven Children's Hospital (YNHCH) from January 1, 1986, through December 31, 2007, and received PET for PHS shortly after birth were included. Neonates who received a PET for anemia or a double volume exchange transfusion for any cause were excluded. One infant with iatrogenic polycythemia was also excluded. Charts from 141 infants who met criteria were reviewed. During the entire study period, the NBSCU at Yale New Haven Children's Hospital was under the same leadership of Dr. Ian Gross and Dr. Richard Ehrenkranz.

Data collection included incidence of PET, patient and maternal demographics, known or suspected risk factors for developing PHS, physician recorded indication for PET, laboratory evaluation surrounding PET, complications possibly related to PHS**,** complications possibly related to PET, and comorbidities of patients receiving PET. In accordance with AAP Guidelines,[72] asymptomatic patients were not screened for polycythemia. Blood viscosity was not measured. Data were collected in a de-identified manner using pre-designed data collection sheets and entered into a Microsoft Access Database for collection, review, and analysis.

In order to conduct longitudinal comparison, groups were divided into two time periods. The *early* time period was January 1, 1986-December 31, 1996 and the *later* time period was January 1, 1997-December 31, 2007. These time periods were chosen as representative samples of obstetric practice, with the mid 1990's representing a time demarking the widespread adoption of numerous advances in

prenatal care including ultrasound, Doppler techniques, fetal heart rate monitoring, cordocentesis, and management of the diabetic pregnancy.[73,74] These changes were summarized in the review by Battaglia and Marconi in 1997 on "the new obstetrics."[73]

Risk Factors for Polycythemia Hyperviscosity Syndrome

Mother and infants were assessed for the following risk factors for PHS: maternal diabetes, maternal hyperthyroidism, maternal smoking, maternal ethanol use, maternal substance abuse, maternal hypertension, pregnancy-induced hypertension, preeclampsia, intrauterine growth restriction, twin-twin transfusion syndrome, fetal trisomy or other genetic syndromes including Beckwith-Weidemann syndrome, maternal fetal transfusion, delivery outside labor and delivery, perinatal asphyxia, delayed cord clamping, nuchal cord, cord stripping, neonatal hypothyroidism, and congenital adrenal hyperplasia.[58,60,63,75-81] The diagnosis of intrauterine growth restriction was assigned using the criteria of Alexander et al.[82]

Indications for Partial Exchange Transfusion

Indications for PET during the study period were: 1) hematocrit of 70% or above with or without symptoms attributable to PHS; 2) hematocrit of 65% or above with symptoms attributable to PHS or; 3) at the discretion of the attending physician because of symptoms attributable to PHS independent of the hematocrit.[2,83] Findings attributable to PHS included plethora, tachypnea, cyanosis, respiratory distress, feeding intolerance, and neurologic symptoms such as tremulousness, jitteriness, lethargy, hypoglycemia, or thrombocytopenia. Data was

extracted from physician procedure notes to determine whether each patient was symptomatic. There was a significant variation in whether capillary, peripheral venous or umbilical venous hct was used in determining whether the child should receive PET.

During the entire 22 year study period, the protocol for partial exchange transfusion was the following: An umbilical venous catheter (UVC) was placed in a low lying position and a peripheral intravenous catheter (PIV) was inserted. An infant's total blood volume was assumed to be 85cc/kg body weight. The volume of exchange, calculated as blood volume x (observed hematocrit – desired hematocrit)/observed hematocrit, was removed via the UVC while infusing the same volume of normal saline via either the PIV or an umbilical line. This technique, performed over an approximately 15 minute period, allows the patient to maintain euvolemia during the entire PET. Upon completion, the UVC was flushed with normal saline and removed unless there are other indications for its continued use. Ten percent dextrose was infused via the PIV for at least the next 6 hours while the patient receives no enteral feeds.

Significant Complications of Polycythemia Hyperviscosity Syndrome or Partial Exchange Transfusion

Complications that were possibly related to PHS or PET were analyzed. PHS-related complications were defined as any known complication of PHS present *prior* to PET. PET-related complications were defined as any complication, not present before PET, which occurred within 7 days after the PET. However, in delayed-type complications like NEC, it was impossible to attribute it to either PET or PHS, and

was counted as a possible complication in both. Complications of PHS or PET were defined as follows:

Apnea: Cessation of respirations for > 20 seconds

Bradycardia: Sustained heart rate < 100 bpm

Tachycardia: Sustained heart rate > 180 bpm

Seizures: Clinical evidence of seizure-like activity treated with anti-seizure medication or EEG-documented seizures

Symptomatic Hypotension: Decline in blood pressure requiring treatment with intravenous fluids or medication

Pulmonary Hypertension: Respiratory distress with evidence of elevated right heart pressures by echocardiography or significant variation in pre- and post-ductal SpO_2

NEC: Modified Bell's criteria $\geq$ stage 2a[4,84-86]

Renal Failure: Urine output < 1 cc/kg/hr for > 24 hours or serum creatinine concentration >1.5 mg/dL

Thrombotic or Ischemic Event: Significant disruption of blood flow due to vessel occlusion from thrombus diagnosed by Doppler ultrasound, contrast angiography, or magnetic resonance angiography

Catheter Malfunction: Catheter thrombosis, rupture or dysfunction

Severe thrombocytopenia: Platelet count < 50,000/mm^3

Hypoglycemia: Blood glucose < 50mg/dL

Hypocalcemia: Serum calcium < 8.0mg/dL or plasma ionized calcium < 3.5mg/dL

Hyperbilirubinemia: elevation of indirect bilirubin requiring treatment with phototherapy or double-volume exchange transfusion without other known causes

Intracranial Hemorrhage: Intracranial detected by ultrasound, computerized tomography or magnetic resonance imaging of the head

PET-Related Mortality: PET-related mortality was defined as any death which was directly related to the PET and occurred within 7 days after the exchange.

Statistical analysis

The SPSS v13.0 statistical software package (SPSS Inc., Chicago, IL) and GraphPad Prism 3.0 (GraphPad Software, Inc., San Diego, CA) were utilized for data analyses. Continuous data were compared using the Student t comparison of means. Dichotomous data were compared using a Pearson's chi-square analysis or Fisher's exact test when at least one cell contained a value <5. Trends were analyzed using linear regression analysis. A p-value of <0.05 was considered statistically significant.

Infant Comorbidities

Significant comorbidities including congenital heart disease, respiratory disease, genetic syndromes, sepsis not related to PHS or PET, IVH, renal disease or other significant morbidities were also collected.

Laboratory Data

Laboratory data were also collected including pre- and post-exchange hematocrit, hemoglobin, and platelet count.

Human Subject Protection

This study was approved by the Human Investigation Committee of the Yale University School of Medicine.

Statement of the responsibilities of the medical student for which this thesis is submitted

Bridget Hopewell was responsible for requesting charts from medical records after a list of patients was generated from a database by another author. She then reviewed all charts and collected data. All questions or concerns about individual charts were presented to other authors for verification and clarification. Ms. Hopewell entered all data into the Microsoft Access Database and together with Duncan Hopewell queried the data to make all reports, tables, and figures except for Figure 6 which required advanced statistical software and data on admissions that was queried and analyzed by another author.

Results

From January 1, 1986 to December 31, 2007, there were 108,147 live births (mean 4915±351 births/year) at Yale New-Haven Children's Hospital (YNHCH) and 18,117 long term admissions, inborn and outborn, (mean 823±56 long term admissions/year) to the YNHCH Newborn Special Care Unit (NBSCU). PET was performed in 169 infants. Twenty eight infants were excluded; 25 who underwent PET for anemia-related conditions or iatrogenic polycythemia, and 3 with incomplete medical records. The study group was composed of 141 patients who underwent PET for PHS shortly after birth.

Patient characteristics are shown in **Table 4**. One hundred nine infants were singletons. Mean gestational age was 37.3 weeks (range 24-42 weeks). Mean birth weight was 2788g (range 680-4980g). Male:female ratio was 1:1. Most patients had generally normal Apgar scores. PET was mostly performed on Caucasian neonates, followed by Hispanic neonates and Black neonates. Neonates were slightly smaller in weight in the later time period vs. the early time period. There was a smaller percentage of Caucasian neonates in the later period. There was also a decrease in the percentage of singletons and an increase in the percentage of multiple gestation patients receiving PET. Finally, there was an increase in the percentage of patients born by caesarian section receiving PET. Over the 22 year period, the number of PET/year/1000 live births was essentially unchanged. A slight downward trend was not statistically significant ($r^2 = 0.082$, $p=0.192$, **Figure 6**). PET was almost always performed in the first twenty-four hours of life. The median time to the first

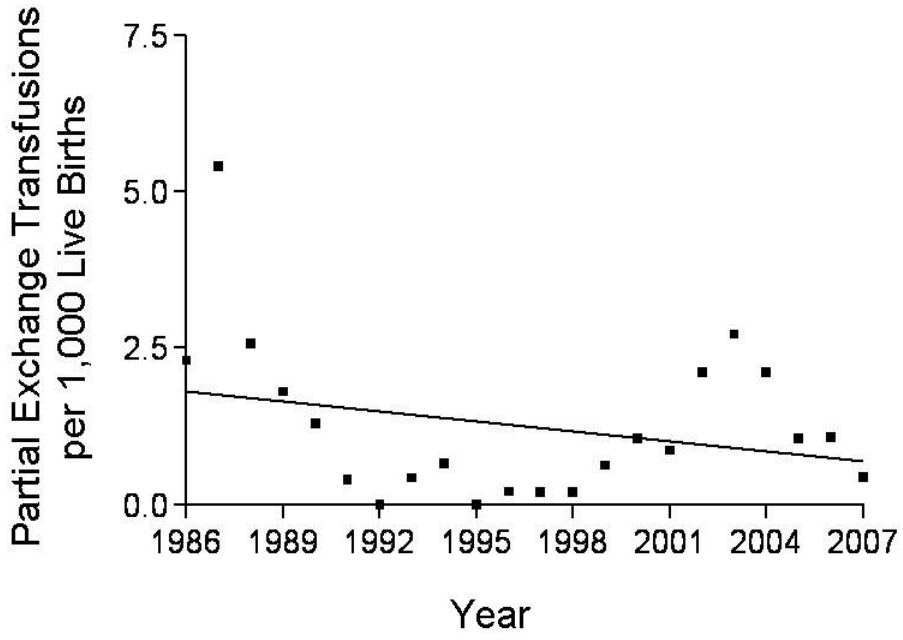
procedure was 9.0 hours. The mean number of hours to the PET, 21.5, was skewed to the right because of some outliers.

Table 4: Perinatal Characteristics and Demographic Factors

Perinatal Characteristics		**All patients**	**1986-1996 N=82**	**1997-2007 N=59**
	Gestational Age (weeks)*	37.3 ± 3.1 (n=138)	37.8 ± 2.5 (n=80)	36.6 ± 3.6 (n=58)
	Birth weight (grams)	2788 ± 871 (n=139)	2977±844 (n=81)	2524±847 (n=58)
	1 minute Apgar ≤5**	16 (11%)	10 (12%)	6 (10%)
	5 minute Apgar ≤7 **	11 (8%)	8 (10%)	3 (5%)
Demographics				
Sex	Male	70 (50%)	42 (51%)	28 (47%)
	Female	71 (50%)	40 (49%)	31 (53%)
Race	White	83 (59%)	54 (66%)	29 (49%)
	Black	11 (8%)	9 (11%)	2 (3%)
	Hispanic	16 (11%)	10 (12%)	6 (10%)
	Asian	2 (1%)	0 (0%)	2 (3%)
	Other	3 (2%)	2 (3%)	1 (2%)
	Not reported	24 (17%)	5 (6%)	19 (32%)
Birth Order	Singleton	109 (77%)	69 (84%)	40 (68%)
	Twin A	7 (5%)	3 (4%)	4 (7%)
	Twin B	18 (13%)	8 (10%)	10 (17%)
	Triplet A	1 (1%)	0 (0%)	1 (2%)
	Triplet C	4 (3%)	1 (1%)	3 (5%)
	Not Reported	2 (1%)	1 (1%)	1 (2%)
Mode of Delivery	Vaginal	96 (68%)	62 (76%)	34 (58%)
	C-Section	45 (32%)	20 (24%)	25 (42%)

** Mean ± Standard Deviation*
*** Number (Percent)*

Figure 6: Partial Exchange Transfusions Over Time.



r^2=0.082, p=0.192

Several risk factors for neonatal polycythemia have been reported. Each patient's chart was reviewed to determine which risk factors most commonly resulted in PHS requring PET at YNHH. The majority of patients (88%) had at least one risk factor for PHS (**Table 5**), with the most common risk factor being maternal diabetes. Other common risk factors included maternal hypertension, fetal trisomy, and unsupervised delivery (**Table 5**). Fifty four neonates (38%) had more than one risk factor. Comparing risk factors between the early and late time periods, there was a statistically significant decrease in maternal diabetes ($p<0.01$) in the later, more recent time period.

Table 5. Perinatal Risk Factors.

*Perinatal Risk Factor**	**Number (Percent)**	**1986-1996 (n=82)**	**1997-2007 (n=59)**
Maternal Diabetes	39 (28%)	29 (35%)	10 (17%)**
Maternal Hypertension	25 (18%)	14(17%)	11 (19%)
Maternal Substance abuse	16 (11%)	9 (11%)	7 (12%)
Maternal Hypothyroidism	2 (1%)	0 (0%)	2 (3%)
Placental Insufficiency	6 (4%)	0 (0%)	6 (10%)
Twin-Twin Transfusion	10 (7%)	4 (5%)	6 (10%)
Nuchal Cord	15 (11%)	11 (13%)	4 (7%)
Unintended Delivery Outside Delivery Room/ Delayed Cord Clamping	14 (10%)	8 (10%)	6 (10%)
Intrauterine Growth Restriction	48 (34%)	23 (28%)	25 (42%)
Fetal Genetic Syndrome	19 (13%)	11 (13%)	8 (14%)
Trisomy 21 15		8	7
Trisomy 13 1		1	0
Other 3		2	1
Other Risk Factors	4 (3%)	4 (5%)	0 (0%)
Any Perinatal Risk Factor	121 (86%)	72 (88%)	49 (83%)

** Number (Percent)*
***p<0.01*

There are no clear, evidence-based guidelines for when to initiate PET. Similar to other centers, in our institution, a PET is initiated for a hematocrit > 70% in the asymptomatic patient or for a hematocrit > 65% with symptoms attributed to PHS.[20] During the study period, 50% of patients (n=71) received a PET because of a hematocrit > 70%. Thirty nine percent (n=55) received a PET because of a

hematocrit > 65% and symptoms attributed to PHS. The remaining patients (11%) underwent PET with a hematocrit between 60-65% and symtoms attributed to PHS. Mean hematocrits before and after PET were 69.7±4.2% and 57.3±5.8%, respectively. In contrast to previous studies which included mostly asymptomatic infants, due to our selection bias, the majority of the patients in our series had at least one clinical sign or symptom attributed to PHS in addition to an elevated hematocrit prior to PET (**Table 6**).[24] The most common findings were hypoglycemia, plethora, tachypnea and jitteriness. Because of the three accepted indications for PET, there was a wide range of hematocrits before and after transfusion as shown in **Figure 7**, but the mean hematocrit before transfusion was 69, and the mean hematocrit after transfusion was 58.

***Figure 7*: Hematocrits before and after PET.**
**The mean hematocrit before PET was 69 and the mean hematocrit after PET was 58*

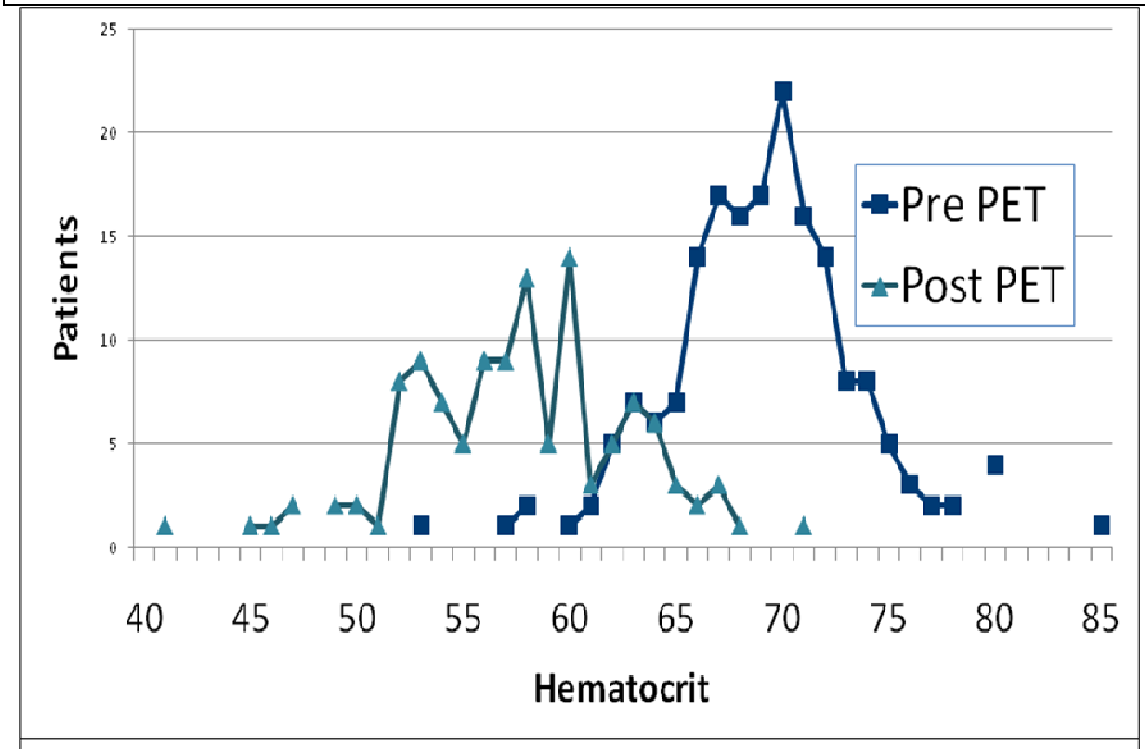


Table 6. Signs and Symptoms Attributed to Polycythemia Hyperviscosity Syndrome Before Perinatal Partial Exchange Transfusion.

Signs and Symptoms	Number (Percent)	1986-1996 (n=82)	1997-2007 (n=59)
Hypoglycemia	41 (29%)	24 (29%)	17 (29%)
Plethora	35 (25%)	22 (27%)	13 (22%)
Tachypnea	19 (13%)	5 (6%)	14 (24%)
Jitteriness	18 (13%)	11 (13%)	7 (12%)
Cyanosis	13 (9%)	8 (10%)	5 (8%)
Thrombocytopenia	8 (6%)	3 (4%)	5 (8%)
Hypotonia	6 (4%)	0 (0%)	6 (10%)
Apnea	4 (3%)	2 (2%)	2 (3%)
Feeding intolerance	4 (3%)	2 (2%)	2 (3%)
Lethargy	4 (3%)	3 (4%)	1 (2%)
Other recorded indication	16 (11%)	3 (4%)	13 (22%)
Any sign or symptom	96 (68%)	51 (62%)	45 (76%)

In addition to the signs and symptoms attributed to PHS described in **Table 6**, several additional clinically significant complications of PHS have been described. These include cardiopulmonary and neurologic problems. In our series, over one third of patients (40%) had significant complications attributed to PHS *prior* to the inititation of PET (**Table 7**) including pulmonary hypertension, necrotizing enterocolitis, thrombotic/ischemic events, and severe thrombocytopenia. Hyperbilirubinemia was the most frequent complication (n=41, 29%). As the

median time from birth to PET was 9 hours, this finding re-enforces the suggestion that polycythemia can cause clinically significant jaundice, even on day of life one.

Table 7: Complications Attributed to Polycythemia Hyperviscosity Syndrome

Complication	**Number (Percent)**	**1986-1996 n=82**	**1997-2007 n=59**
Hyperbilirubinemia	41(29%)	26 (32%)	15 (25%)
Pulmonary Hypertension	8 (6%)	4 (5%)	4 (7%)
Necrotizing Enterocolitis	5 (4%)	2 (2%)	3 (5%)
Thrombotic/Ischemic Event	2 (1%)	0 (0%)	2 (3%)
Thrombocytopenia	2 (1%)	0 (0%)	2 (3%)
Any Complication	56 (40%)	32(39%)	24 (41%)

Few studies have examined the complications associated with PET, and those studies have focused on the GI complications, most notably necrotizing enterocolitis (NEC). In our study, PET-related complications were common, occurring in 25 patients (18%) (Table 5). The most common were catheter-related complications. Other life-threating complications of PET were rare, but did occur (including sepsis and hypotension, **Table 8**). Similar to previous studies,[67] we found an increased incidence of NEC after PET. Because PHS alone is a risk factor for NEC, it is impossible to determine if NEC would have occurred if PET had not been carried out. There were no statistically significant differences in complications between the two time periods studied.

Table 8. Complications Attributed to Partial Exchange Transfusion

Complication	Number (Percent)	1986-1996 n=82	1997-2007 N=59
Catheter Complication	10 (7%)	4 (5%)	6 (10%)
NEC	5 (4%)	2 (2%)	3 (5%)
Thrombocytopenia	8 (6%)	2 (2%)	6 (10%)
Suspected or Proven Sepsis	5 (4%)	5 (6%)	0 (0%)
Hypotension	1 (1%)	1 (1%)	0 (0%)
Any Complication	25 (18%)	8 (10%)	17 (29%)

Discussion

These data demonstrate that PET for PHS continues to be a common procedure at YNHCH, without evidence for decline over two decades, representing the longest single-center, longitudinal documentation of trends in PET. They also document that the patient population undergoing PET was generally term neonates with one or more risk factors for PHS. A large number of patients had clinical symptoms consistent with PHS prior to PET. Since the AAP recommends against screening asymptomatic patients for polycythemia,[72] our symptomatic patient population is likely representative of the majority of infants who currently undergo PET for PHS, yet previous studies of PET for PHS have focused on asymptomatic infants.[66,87]

There are no randomized, controlled studies of the efficacy of PET done in *symptomatic* infants, and it is difficult to generalize studies of efficacy done on largely asymptomatic infants to a symptomatic popoulation. Although further studies of PET in symptomatic patients are necessary to determine whether PET provides a clinically significant, long term benefit, monitoring of high-risk populations to identify infants with symptomatic PHS is critical. Multiple studies have demonstrated that symptomatic patients with PHS are at risk for adverse neurologic outcomes,[53,55,69] highlighting the need for careful developmental follow-up of these infants even if they do not undergo PET. These data are consistent with the hypothesis that in some patients, an adverse intrauterine environment or a significant perinatal event leads to tissue hypoxia, polycythemia, hyperviscosity, and irreversible tissue damage that would not be ameliorated by PET.[7,66,69] Future

studies to compare infants with PHS caused by an adverse intrauterine environment leading to hypoxia and tissue damage with infants developing PHS because of a one-time insult at birth like delayed cord clamping may be illuminating.

The literature contains very little information regarding the safety of PET. A meta-analysis has demonstrated an increased risk of NEC following PET,[67] but studies specifically detailing adverse events related to PET have not been done. Although the majority of the complications associated with PET in this series were minor, serious complications were observed. The possiblity of serious complications from PET supports the practice of not doing PET on asymptomatic infants, who are unlikely to benefit from the procedure.

The lack of data regarding the risks and benefits of PET makes it difficult to determine when to initiate a PET and the threshold hematocrit at which to perform a PET.[88] The standard of care in many nurseries, outlined by Linderkamp,[20] is to perform a PET when the venous hematocrit is ≥ 65% in an infant with symptoms of PHS or when the venous hematocrit is ≥ 70% in an asymptomatic infant, although there are little data to support this approach. In other institutions, PET is not performed in asymptomatic neonates until the hematocrit is $\underline{\geq}$ 75%. Part of the controversy over the threshold hematocrit stems from the fact that hematocrit is an imprecise method of determining blood viscosity and may be a poor indicator of who needs a PET. Polycythemia and hyperviscosity are not synonymous terms and many factors in addition to hematocrit, such as plasma proteins, leukocytes, fibrinogen, platelets, blood pH, and erythrocyte deformability can affect blood viscosity.[16,17,23,24,38,56] Direct measurement of blood viscosity, measured using a

whole blood viscometer, is often not available in the clinical setting and thus the hematocrit is used as a surrogate marker. However, hematocrit is an imperfect measure of viscosity, as not all infants with an elevated hematocrit have increased blood viscosity.[89] Given the risk of complications from both PHS and PET, a more precise test of blood viscosity is needed to better determine which patients might benefit from PET.

As risk factors for PHS are diverse and include an unfavorable uterine environment leading to tissue hypoxia, endocrine abnormalities, genetic abnormalities as well as transfusion of erythrocytes, it is possible PHS is a more heterogeneous population. As such, it is currently unclear whether the different risk factors for developing PHS lead to different outcomes, and would respond differently to PET. It has been hypothesized that poor developmental outcomes are more related to a hostile uterine environment which also causes polycythemia, and thus would not respond to PET.[67] Perhaps patients with PHS which develops from a harsh uterine environment and infants with PHS associated with erythrocyte transfusion represent separate populations. A meta-analysis showed that delayed cord clamping by 2 minutes after birth did cause an increase in polycythemia that appeared to be asymptomatic.[76] Our sample sizes were not large enough to separate and compare these different populations, but it is an area for further study.

Additional factors contributing to the controversy in decision making in PHS include a lack of standardized diagnostic criteria for PHS, inconsistent study methodology, and variability in the methodology utilized for PET. Data are not available to determine whether reducing the hematocrit leads to improvements in

long term outcome, as well controlled studies comparing long term follow up in symptomatic and asymptomatic infants treated with PET to those treated expectantly, are not available.

Our data exemplify the advantages and disadvantages of single-center observational studies. The longitudinal collection of data over more than two decades has allowed us to analyze trends in treatment of PHS with PET over time. Limitations of this study include its retrospective nature, relatively small sample size, lack of long term developmental follow up data, and a lack of a specific control group for these patients. We have tried to clearly define complications from PHS and PET. However, due to the large amount of overlap in symptomatology, it is impossible to truly define a complication as resulting entirely from PET, as PHS may have also contributed to its occurrence. It is also possible that complications attributed to PHS or PET were due to other unknown causes, especially since our population consisted of complex patients admitted to the NBSCU. It should therefore be recognized that complications cannot be attributed with absolute certainty within the limits of this retrospective chart review. Confounding is therefore possible in our study, and further controlled investigation into complications could help elucidate the attributable risk of complications specific to PHS and PET.

We conclude that PHS remains a common problem, particularly in at-risk populations. Both PHS and PET are associated with clinically significant complications. Despite its frequency, treatment of PHS with PET remains

controversial. Additional controlled studies with long term follow up are needed to assess the benefits of PET for PHS.

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