Rapid bilateral pulmonary artery banding: A developmentally based proposal for the management of neonates with hypoplastic left heart

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“We cannot solve our problems with the same thinking we used when we created them.”

–Albert Einstein

“For things to reveal themselves to us, we need to be ready to abandon our views about them.”

–Thich Nhat Hahn

Since the description of hypoplastic left heart syndrome (HLHS) by Noonan and Nadas in 1958, and the seminal publication of surgical intervention by Norwood, Lang, and Hansen in 1982, 1 outcomes have improved remarkably from a universally fatal lesion to one where there are now survivors in their fourth decade of life. 2 Key elements in the maturation of surgical therapies and medical management have included modifications of the original Norwood operation, including techniques for arch reconstruction and options to provide pulmonary blood flow; 3 improved anesthesia and cardiopulmonary bypass (CPB); 4 improved understanding of the multidistribution circulation; 5 hybrid palliation for high-risk patients; 6-12; a “deferred Norwood” strategy 13 (bilateral pulmonary artery banding [PAB] and prostaglandin); improvements in interstage monitoring 14,15, an interim superior cavopulmonary connection (SCPC); 16 modifications of the Fontan operation 17-19; and a better understanding of the longer-term consequences of the Fontan circulation/total cavopulmonary connection. 20-22 Finally, although neonatal heart transplantation remains a viable surgical option, limited donor availability renders this strategy as a primary mode of surgical therapy impractical for the majority of patients.

CENTRAL MESSAGE

Rapid bPAB within 48 hours of birth will mitigate the reduction of systemic oxygen delivery due to circulatory maldistribution that occurs immediately during the transitional circulation in HLHS.

See Commentary on page XXX.

In the context of these remarkable improvements in the past 40+ years, several management controversies currently exist and are subject to considerable debate and disagreement among practitioners caring for these neonates—both between and within cardiac programs. Most importantly, these include type of initial procedure (hybrid vs Norwood); optimal timing of the Norwood operation; practices to maximize systemic oxygen delivery, both before and after surgery; and the routine use of delayed sternal closure, among others. Many of these controversies have evolved due to the unstable physiology present, particularly during the 2 most vulnerable periods for these babies—immediately after birth and immediately after surgery.

CURRENT RESULTS OF INTERVENTION FOR HLHS AND VARIANTS

It must be emphasized that any comparison of surgical mortality rates is confounded by the risk profile of the patients who undergo the various surgical options. With this important caveat in mind, the cumulative mortality rate
for the Fontan pathway—the classic Norwood operation during the neonatal period, combining early (~10%),23 interstage (~10%),23 SCPC/bidirectional Glenn, and Fontan (1%-6% and 1%-3%) have resulted in longer-term survival rates that have plateaued around 60%.3,24,25,E1 The hybrid operation, used at some centers as a primary procedure for all patients, as well as at many centers for patients at increased risk, has been reported at approximately 78% survival at 10 years (see Table 1).E13-E15 The deferred Norwood strategy, most commonly utilized in Japan, has been reported to have a 6-year transplant-free survival rate of 84.5%.E16

In addition to among the highest surgical mortality rates in congenital cardiac surgery, most of these patients typically have long hospitalizations, with the median length of hospitalization between >7-8 weeks, E17,E18 including some with longer lengths of stay that include the SCPC on the same admission. Complications are common, including consequences of invasive catheters, mechanical ventilation, injury to the recurrent laryngeal and phrenic nerves, infection, necrotizing enterocolitis, unplanned procedures, and many more (see Table 1). In addition to these short-term consequences, these complications can also contribute to long-term challenges such as ventricular dysfunction, atrioventricular valve regurgitation, vascular access limitations, neurodevelopmental challenges, chronic kidney disease, hypertension, proteinuria, gastrointestinal complications, and abnormal lung function. E20,E28,E33-E35,E37 Considering the high mortality and morbidity subsequent to surgical intervention for HLHS, the need for a fundamental change in the management of these patients should be considered, utilizing the components of all 3 currently used approaches, with a specific emphasis on minimizing morbidity as well as improving short-term survival.

Some patient-related risk factors for mortality and short- and long-term morbidity are nonmodifiable, such as low weight, prematurity, additional congenital anomalies, and genetic syndromes. However, there are 2 particularly high-risk periods for a neonate with HLHS where a change in strategy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Norwood procedure</th>
<th>Hybrid stage I</th>
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<tbody>
<tr>
<td></td>
<td>STS23</td>
<td>STS</td>
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<tr>
<td>Hospital mortality (%)</td>
<td>7/1/16-6/30/20</td>
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<tr>
<td></td>
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<td>1/18-12/21</td>
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<td></td>
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<td></td>
<td>SVR trial,45,47</td>
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<tr>
<td>Unplanned reintervention (%)</td>
<td>Surgical 16%</td>
<td>Surgical 22%</td>
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<tr>
<td></td>
<td>Catheterization</td>
<td>Catheterization</td>
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<tr>
<td></td>
<td>5.4</td>
<td>6.5</td>
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<tr>
<td></td>
<td>16</td>
<td>16</td>
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<tr>
<td>Cardiac arrest (%)</td>
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<td>23</td>
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<tr>
<td>ECMO (%)</td>
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<tr>
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<td>Vocal cord injury (%)</td>
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<td>Nasogastric or gastrostomy tube</td>
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<td>at discharge (%)</td>
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<td>Mean 59</td>
<td>Median 60</td>
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<td></td>
<td>Median 47</td>
<td>Note: 9.4%</td>
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<tr>
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<td>until SCPC</td>
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STS, Society of Thoracic Surgeons; PC4, Pediatric Cardiac Critical Care Consortium; NPCQIC, National Pediatric Cardiology Quality Improvement Collaborative; SVR, single ventricle reconstruction; ECMO, extracorporeal membrane oxygenation; SCPC, superior cavopulmonary connection. *PC4 specific definitions: newer PC4 sites contributed data for less than the specified date range; Norwood procedure and hybrid stage I included if index operation; cardiac arrest, ECMO, renal replacement therapy, neurologic injury, vocal cord injury all postoperative; renal replacement therapy only for acute kidney injury not prophylaxis; vocal cord injury before February 1, 2019, only diagnosed while still in cardiac intensive care unit, diagnosis is endoscopic; hypoxic ischemic encephalopathy included with stroke. E13-E15,NPCQIC data combines Norwood and hybrid data, and excludes anyone who transitioned to biventricular physiology, or who was deemed not a candidate for Comprehensive Stage II palliation. Mortality is Norwood-specific. E13-E15,Mortality is hybrid-specific.
is modifiable and may improve outcome: during the transi-
tional circulation and during the early postoperative period.
The currently utilized care strategies during these time frames
vary considerably across care teams, and lend themselves to
both standardization and patient-specific application.
Thus, given the suboptimal short- and long-term results, we
are proposing a fundamental change in strategy to minimize
morbidity and mortality during these two time frames, utiliz-
ing currently available techniques: rapid bilateral PAB
(bPAB) during the first 24 to 48 hours of life with continued
use of Prostaglandin, and abandoning the Norwood procedure
in the neonatal period whenever possible. This approach is
proposed, in part, due to a better understanding of the vulner-
ability during the transitional circulation, coupled with an in-
depth understanding of the developmental biology of the
heart as well as all other organ systems in the neonate.

DEVELOPMENTAL PHYSIOLOGY FOLLOWING
BIRTH IN NEONATES WITH STRUCTURALLY
NORMAL HEARTS

Heart
After birth, following the fall in pulmonary vascular resis-
tance (PVR) and the closure of the ductus arteriosus, the
afterload of the right ventricle (RV) decreases signifi-
cantly, the RV dominance regresses rapidly in the first 48 hours
of life, and RV mass is expected to stabilize around age 3 to
4 months. During the first 2 weeks after birth, as
pressure and volume workload change, the systemic left
ventricle accommodates pressure changes via cellular
hyperplasia and angiogenesis (cardiomyocyte proliferation)
rather than hypertrophy. Animal studies also suggest a
maximal enhancement in contractility and relaxation within
the first 8 postnatal days. In summary, the ability during the transitional circulation, coupled with an in-
depth understanding of the developmental biology of the
heart as well as all other organ systems in the neonate.

Brain
The production and migration of neurons are largely pre-
natal events, reaching a peak at 28 weeks’ gestation. However, proliferation and migration of glial progenitors
and differentiation of astrocytes and oligodendrocytes con-
tinues for an extended period after birth. Apoptosis be-
gins in the second trimester, but continues throughout the
first year of life, as does synaptogenesis (ie, connectivity),
oligodendrogenesis, axon growth, and myelination. These
metabolically active areas of brain growth are partic-
ularly susceptible to hypoxic-ischemic injury.

Kidneys
At birth, there are rapid changes in plasma flow to the kid-
ney, filtration at the glomerular level (ie, glomerular filtra-
tion rate [GFR], drug metabolism, and toxin elimination).
Renal function is low at birth, (GFR ~20-39 mL/min/
1.73 m²) with a continued rise during the first 4
weeks. Factors contributing to the maturational increase in GFR include increase in filtration surface area
and glomerular permeability as well as an increase in
arterial pressure and renal blood flow. The literature shows
high variability in the estimates of both effective renal plasma flow as well as GFR. In general, GFR doubles
during the first 5 days after birth, from 19.6 to 40.6 mL/min
per 1.73 m², and then more gradually increases to 59.4 mL/
min per 1.73 m² by age 4 weeks. Adult levels of GFR may
not be reached until 1 year of age.
By day three, mucosal mass increases by 115%, intestinal
length by 24%, and intestinal diameter by 15%.
In a human fetus, the intestine is filled with sterile amni-
otic fluid and the initiation of microbial colonization begins
with oral intake of milk on postnatal day one. This first
exposure to microorganisms and environmental endotoxins
is followed by a crucial sequence of active events necessary
for immune tolerance and homeostasis. The initial gut col-
ization influences the future gut microbiota, and the gut
microbiome demonstrates accelerated maturation during
the first year. During the first 2 weeks, the intestinal
epithelium develops to tolerate colonizing bacteria, such
as secretion of neonate-specific antimicrobial peptides and
constitutive active downregulation of the innate immune
TLR4 pathway. Goblet cells, which serve an innate bar-
errier function, do not reach the tips of the villi for at least 1
week after birth. There is a close interplay between the ma-
jor cell types lining the intestine, nutrients, and the micro-
bacteria, which are all constituents of the intestinal
ecosystem. Thus, the risk of intestinal injury and perme-
ability are at their highest shortly after birth, and are partic-
ularly susceptible to abnormalities in blood flow, oxygen
delivery, and lack of enteral nutrition.

Lung
The lung parenchyma and vasculature are both immature
at birth. Although the number of airway generations is
nearly complete at birth, the morphology of the pulmonary parenchyma subsequently transforms greatly in later infancy and childhood. Only approximately 85% of the alveoli are formed after birth, and the lung parenchyma contains several generations of transitory ducts that end in sacculles, which will later develop into alveoli. Parallel to the augmented alveoli formation, alveolar surface area increases significantly within the first year of life and the increased number of alveoli per unit area is also confined to early infancy. In addition to the gas-exchange function of the lungs, the extremely rapid changes in pulmonary vascular resistance have been well described, and will not be repeated here. Although not measured in human newborn infants, the fall in PVR is measured in seconds—not hours or days—in newborn lambs.

THE FETAL AND EARLY TRANSITIONAL CIRCULATION IN NEONATES WITH HLHS

During fetal life, the combined cardiac output (CCO) from the single RV is only mildly decreased compared with the CCO in a fetus with a structurally normal heart. In contrast to a neonate with a structurally normal heart where the RV and left ventricle outputs are equal after ductal closure, the RV must support the multidistribution circulation: systemic blood flow, plus the pulmonary blood flow, plus any tricuspid regurgitant volume (if present). Thus, in HLHS, CCO increases rapidly during the first few days of life, by a combined increase in stroke volume and heart rate. In contrast to a normal heart, the relative contribution and changes from hyperplasia to hypertrophy early after birth in HLHS is unknown. However, this acute change leads to a volume-mass mismatch, and we speculate that this may be a factor contributing to an increase in tricuspid regurgitation in some neonates. Due to the concomitant changes in heart rate and stroke volume, the volume workload of the RV increases immediately, whereas the acquisition of ventricular mass is delayed. Although not studied in neonates with HLHS, rapid increases in RV mass due to increased afterload have been demonstrated within 4 days in lambs and a similar finding of rapid mass acquisition of the left ventricle has been observed in neonates undergoing the rapid 2-stage arterial switch operation for transposition of the great arteries.

Pulmonary blood flow continues to increase as PVR falls, whereas the opposite occurs with systemic blood flow. Recent work by Eckersley and colleagues demonstrated that systemic blood flow is abnormally low within 6 hours of postnatal life, and continuously decreases to about half of the normal values during the first 4 days of postnatal life. During this period, significantly higher middle cerebral artery and celiac artery pulsatile indexes are also observed, consistent with elevated cerebral and intestinal vascular resistance and reduced cerebral and intestinal blood flow, confirmed by decreased flow in the superior vena cava.

Indeed, cerebral blood flow and oxygen delivery falls, and cerebral oxygen extraction rises daily during the transition while awaiting surgery, and most likely contributes to the long-term neurodevelopmental disabilities so common in this population.

In neonates with HLHS, although systemic blood flow is low almost immediately after birth, the clinical manifestations of low systemic blood flow—including tachycardia, tachypnea, lower blood pressure, rising lactic acid values, falling near-infrared spectroscopy values, increased risk of necrotizing enterocolitis, and decreasing urine output—only become apparent over the subsequent 2 to 7 days or so. Concurrently, the increased pulmonary blood flow can result in tachypnea, carbon dioxide retention, respiratory failure, and pulmonary edema. A variety of interventions can be performed to redistribute the combined cardiac output preferentially to the systemic circulation, including endotracheal intubation and mechanical ventilation with sedation and neuromuscular blockade to decrease oxygen consumption, increasing positive end-expiratory pressure, and other techniques to increase PVR such as subatmospheric oxygen and hypercarbic gas mixtures, blood transfusions to increase oxygen delivery, and vasoactive agents such as milrinone for reducing systemic vascular resistance. All of these interventions carry potential morbidity, and very few of these have been studied under randomized conditions during the preoperative period. Nonetheless, a number of centers routinely use these strategies during the preoperative period.

RELATIONSHIP OF DEVELOPMENTAL IMMATURITY, PREOPERATIVE MANAGEMENT OF THE TRANSITIONAL CIRCULATION, AND CPB ON POSTOPERATIVE OUTCOMES

In neonates and infants, a low cardiac output state has been demonstrated for at least 24 to 36 hours after surgery. In addition to the low GFR due to preexisting immaturity of the kidneys discussed above, GFR has been shown to be even lower (<30 mL/min/m²) after CPB in patients with biventricular circulations. Although GFR has not been measured following stage 1 Norwood surgery, the incidence of acute kidney injury is high. Central nervous system abnormalities are common, such as a 10% to 20% risk of seizures, increased white matter injury, stroke, and hemorrhage, as described in Table 1.

From a developmental perspective, it is not surprising that—in addition to among the highest surgical mortality rates in the entire spectrum of congenital heart disease—there is a significant amount of cumulative morbidity following either the hybrid or Norwood procedures in the...
The median length of hospital stay is about 2 months, but may be much longer, considering half of the hospital survivors. tube feedings are necessary after discharge for at least enterocolitis. Enteral/oral feeding is often delayed, and anasarca, acute kidney injury, seizures, and necrotizing enterocolitis. Enteral/oral feeding is often delayed, and tube feedings are necessary after discharge for at least half of the hospital survivors. The median length of hospital stay is about 2 months, but may be much longer, considering the superior cavopulmonary connection takes place during the same hospitalization in ~10% of patients (see Table 1). Familial well-being and in particular maternal mental health may also be seriously compromised, with lifelong effects.

PROPOSAL

We propose early bPAB within 24 to 48 hours of life and deferral of the Norwood procedure beyond the neonatal period. We speculate that near-immediate or rapid bPAB will significantly improve the circulatory maldistribution, which should then allow for improved organ maturation, including appropriate ventricular maturation and myocardial hyperplasia/hypertrophy, less tricuspid regurgitation, and less congestive heart failure during the early neonatal period. Additional benefits will include the early institution of neurodevelopmental care and maternal bonding, a lower risk of seizures after CPB, improved family well-being, an increase in renal blood flow and GFR, oral feeding, improved nutritional status, maturation of the immune system, and more.

Compared with bPAB in a classic hybrid approach, with an anticipated period of 4 to 6 months before a comprehensive stage 2, the bPAB for a deferred Norwood should be considerably more restrictive if a period of 4 to 6 weeks of banding is anticipated. This tight bPAB approach is likely to improve circulatory maldistribution more rapidly, but result in earlier progression of hypoxemia as the baby grows.

Given the emerging data on the rapidity of onset of end-organ ischemia during the early transitional circulation, we believe that rapid restriction of the pulmonary flow is warranted. This strategy should minimize the documented fall in global systemic blood flow, and improve oxygen delivery to the coronary arteries, myocardium, brain, kidney, and gut.

Additionally, rapid bPAB will provide near-normal systemic oxygen delivery during the time that is necessary to evaluate the anatomy and myocardial function, the brain, all other organs, perform a genetic consultation if indicated, further counsel parents and obtain informed consent, while decision making is undertaken for the next steps. We speculate that this approach will decrease the likelihood of intensive care unit interventions frequently employed before surgery; such as intubation, mechanical ventilation, change in inspired gases, inodilators, lack of enteral feeding, central venous access, and parenteral nutrition. There is evidence that the performance of bPAB (age 5-7 days), even in a heterogeneous population of neonates with HLHS, can be accomplished with early survival rates above 95% and extremely low morbidity. There is every reason to believe that even earlier banding will have similar success.

Compared with the recovery from a Norwood procedure in the first week of life, postponing the Norwood procedure with CPB and myocardial ischemia beyond the neonatal period allows the recovery to take place in a baby with more physiologic stability, having received healthy newborn infant care, and developing organ maturity. In a small series, with a deferred Norwood following bPAB at a mean of age 7 days, Ota and colleagues reported lower peak lactate values and higher urine output after the deferred Norwood compared with those who had a primary Norwood during the neonatal period.

Finally, it is important to emphasize that, following rapid bPAB, either the hybrid approach or deferred Norwood approach may still be taken, no “bridges are burned”. The next-step decision can be based on patient factors, cardiologist or surgeon preference, and/or institutional experience (see Figure 1).

POTENTIAL CONSEQUENCES AND UNANSWERED QUESTIONS

Our proposed approach is, admittedly, theoretical at this point, and there are a number of unknowns to be considered. By surgically placing PABs in all patients, the Norwood by definition becomes a re-do operation. Will this result in a more technically challenging procedure? Will surgical adhesions result in more bleeding, or more frequent injury to the recurrent laryngeal and/or phrenic nerves? Will CPB times be increased? Will the cerebral and coronary circulations be adequately maintained on prostaglandin, particularly with aortic atresia? Although there are the many proposed benefits from early PAB and delayed Norwood operation described above, what will be the unintended consequences of 4 to 6 weeks in hospital? All of these are testable hypotheses.

It should be mentioned that an additional possibility to achieve the same physiologic result as we propose would
The authors reported no conflicts of interest.

Conflict of Interest Statement
The authors reported no conflicts of interest.

CONCLUSIONS AND NEXT STEPS
The current short- and long-term results of surgical intervention for HLHS, although gratifying in the historical sense, remain unsatisfying. We can and must do better with respect to short- and long-term survival rates, minimizing cumulative hospital morbidity, and improving quality of life for patients and their families over the long-term. As we learn more about the fetal circulation in HLHS, the immediate consequences of the transitional circulation, and revisit the well-described developmental immaturity present at birth, we believe that our proposal of rapid bPAB within 48 hours and a delayed Norwood procedure as these new approaches on a heterogeneous patient population are implemented.

be the use of catheter-based PA flow restrictors. This approach would allow the Norwood to be performed as a first operation/sternotomy; however, the effects of the flow restrictors on physiology and PA growth would need to be similarly assessed. We need consistent and standardized assessments of cardiac, cerebral, renal, and intestinal function before and after the Norwood procedure as these new approaches on a heterogeneous patient population are implemented.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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References


Key Words: hypoplastic left heart syndrome, pulmonary artery banding, hybrid hypoplastic left heart syndrome
E-References


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