The survival of patients with congenital heart disease (CHD) has significantly improved during the past several decades (the Figure). This accomplishment is directly attributable to the net effect of individual therapeutic successes from the innovative work of surgeons and cardiologists and the courageous devotion of patients and families. However, as the field moves forward, the need for evidence-based medicine derived from multi-institutional collaborations to address more subtle and complex questions such as functional outcome and quality of life and to provide data to guide individual practitioners has become paramount. Recognizing this, the National Heart, Lung, and Blood Institute (NHLBI) established the Pediatric Heart Network (PHN) in 2001 to provide a collaborative platform for conducting clinical studies.

The need for evidence-based care and the ability of the PHN to provide this evidence were demonstrated by recent developments in the surgical management of hypoplastic left heart syndrome. Hypoplastic left heart syndrome was a uniformly fatal defect before Norwood’s innovative surgical approach in which the diminutive aorta is reconstructed using the pulmonary artery trunk and pulmonary blood flow is provided by a right ventricle to pulmonary artery shunt has seen renewed interest.3 This modification has been widely adopted but has yielded conflicting results.4–7 In May 2005, the PHN launched the Single Ventricle Reconstruction (SVR) trial, a randomized trial comparing these 2 surgical strategies.8 In just over 3 years, 555 infants were randomized at the main PHN and auxiliary sites to complete the trial. Both the number of patients with single-ventricle physiology recruited and the confirmation that certain clinical surgical questions are amenable to a multicenter randomized trial represent important milestones for the field.

Beyond the primary question of the trial, there was recognition that a wide gap in knowledge exists on the impact that everyday decisions have on the surgical management and outcome of patients with CHD. To help identify and define the areas in which clinical studies may have the greatest impact on clinical practice and outcomes, the PHN convened a perioperative working group meeting in April 2009 in Bethesda, Md. The working group was charged with informing the PHN and NHLBI about key clinical problems in the surgical and perioperative care of individuals with CHD; making recommendations about clinical research that the PHN can conduct to address the problems identified; and making recommendations about additional clinical studies, data, and resources required to conduct perioperative research.

The working group identified 4 broad challenges in the perioperative management of patients with CHD, which are listed below with corresponding recommendations and are discussed more fully in the remainder of this article.

- The effects of cardiopulmonary bypass on early recovery and long-term sequelae such as neurodevelopmental deficits remain significant issues for neonates undergoing surgery for CHD. Recommendation: Clinical trials aimed at evaluating novel therapies to address these problems should be a top priority.
- Genetic and genomic factors are likely to be important contributors to outcome but are poorly understood. Recommendation: Systematic collection of patient samples and phenotypic information should be incorporated into all new clinical trials.
- Technology advances in imaging, neuromonitoring, genotyping, devices, and database integration are insufficiently...
Antithrombin III supplementation for cardiopulmonary bypass

Anticoagulation is essential for cardiopulmonary bypass and is typically accomplished with unfractionated heparin. Heparin amplifies the activity of antithrombin III, which catalyzes the inactivation of thrombin and other clotting factors. Infants <6 months of age have decreased antithrombin III levels, and further decreases are noted in children with CHD. Therefore, heparin may not achieve adequate anticoagulation, and disorders in hemostasis and thrombosis and an exaggerated inflammatory response may occur. Preliminary data from a small randomized clinical trial in adults undergoing cardiopulmonary bypass suggest that antithrombin III supplementation results in less hemostatic activation and decreased markers of postbypass inflammation. In another randomized trial, antithrombin III supplementation restored heparin responsiveness and reduced hemostatic activation in heparin-resistant adults compared with fresh-frozen plasma. No significant safety concerns arose in either of these trials. A phase II trial of antithrombin III supplementation or other hemostatic strategies in infants <6 months of age undergoing cardiopulmonary bypass could provide preliminary safety, efficacy, and mechanistic data. If encouraging, the results of the trial could be used to plan a phase III trial with clinical end points.

Remote Ischemic Preconditioning

Arresting and reinitiating circulation results in ischemia/reperfusion injury. Transient periods of nonfatal organ ischemia induce an innate response that subsequently protects or preconditioning against more profound ischemia in that organ. More clinically relevant is the ability to protect the target organ by remote ischemic preconditioning. In humans, transient limb ischemia, induced by serial inflations of a blood pressure cuff, has been shown to prevent endothelial dysfunction and to downregulate proinflammatory genes. A pilot study has demonstrated that remote ischemic preconditioning reduces biomarkers of myocardial and lung injury in children undergoing open heart surgery. A phase II trial is currently underway in children; the data from that trial should be available in mid 2010 and will help determine whether a definitive trial should be undertaken.

Cardiopulmonary Bypass and Neurodevelopment

Cardiopulmonary bypass and deep hypothermic circulatory arrest (DHCA) have been implicated in one of the most important long-term morbidities suffered by children undergoing surgery for CHD: neurodevelopmental disabilities. Although significant progress has been made in defining the incidence and severity of neurodevelopmental problems in the CHD population, many issues remain. These include elucidation of the relative contribution of and interaction between the causal factors, identification of modifiable perioperative risk factors, definition of early valid surrogate variables (eg, brain magnetic resonance imaging [MRI] and EEG findings), and standardization of assessment and follow-up modalities (eg, MRI, neuromonitoring data, neurodevelopmental testing, and functional outcomes). Although it is clear that the causes of the neurodevelopmental problems are diverse and complex, there is general agreement that the perioperative period is an important time of risk, and much more research is needed in this area.

Neurological Outcomes in Early Versus Late Repair of Tetralogy of Fallot

Recent data suggest that brain development is delayed in newborns with CHD relative to newborns at the same gestational age without cardiac defects. This finding suggests that avoiding the insult of cardiopulmonary bypass during the potentially vulnerable neonatal period may improve neurodevelopmental outcome in these patients. Alternatively, it is possible that early brain plasticity may be protective. A natural experiment that could help answer these questions derives from 2 current strategies for repair of tetralogy of Fallot. One strategy is complete repair in early infancy, requiring cardiopulmonary bypass during a poten-
tially vulnerable period; the other is an aorta-to-pulmonary artery shunt in early infancy, followed by complete repair in later infancy during a potentially less vulnerable period. A comparison of neurodevelopmental outcomes with these 2 scenarios could provide mechanistic and outcome data on the relative effects of bypass and long-standing hypoxemia on the newborn brain. Important limitations of such a study would be selection bias and the inability to control for confounder variables.

Linking Existing MRI and Other Neuromonitoring Information With Existing Neurodevelopmental Assessments

Many clinical centers routinely conduct neuromonitoring, including near-infrared spectroscopy, during the perioperative period. Brain MRIs and neurodevelopmental assessments are common components of clinical studies. A multicenter study could link existing data with neurodevelopmental assessments and relevant clinical data, which could identify novel surrogate markers and guide future prospective studies. In addition, conducting such a study could help facilitate standardization of neuroimaging and neurodevelopmental assessments.

Regional Cerebral Perfusion Versus DHCA

DHCA, used to maintain a bloodless and motionless surgical field during aortic arch reconstruction, requires cooling the patient to 18°C and stopping corporal and cerebral blood flow. DHCA in infancy has been associated with decreased IQ and with behavioral and other developmental abnormalities. Regional cerebral perfusion (RCP) involves directing blood flow continuously to the brain throughout the procedure and has been described as a neuroprotective alternative to DHCA. RCP has been adopted widely. However, a single-center randomized trial demonstrated no improvement in developmental outcome, and another study suggested that RCP may cause worse brain MRI outcomes. Furthermore, RCP methods vary significantly with regard to flow rates, neuromonitoring strategies, temperatures, and pH management. A randomized phase III clinical trial comparing RCP with DHCA would determine which technique, if any, provides superior neuroprotection for children undergoing aortic arch reconstruction on bypass.

Challenge: Genetic and Genomic Factors

In addressing the determinants of perioperative outcome, attention has typically focused on modifiable risk factors (eg, surgical technique, bypass strategies). However, recent evidence suggests that patient factors may play a significant role in predicting outcome. Genetic syndromes and extracardiac congenital anomalies have been shown to predict increased mortality and adverse perioperative outcomes. The chromosome 22q11.2 deletion syndrome has been demonstrated to be a significant risk factor for diminished neurodevelopmental outcome. More subtle genetic variations such as apolipoprotein E genotype may also be important determinants of neurological and behavioral outcomes.

These findings help explain the well-described clinical scenario in which 2 patients with identical congenital heart defects and identical risk factors respond differently during the perioperative period. How genetic variability modifies individual patient response to physiological perioperative stressors is poorly understood. The nascent field of “perioperative genomics” has begun to uncover biological associations between genetic variability and clinical outcomes. For instance, polymorphisms in inflammatory mediators such as interleukin-6, interleukin-10, and tumor necrosis factor-α and in platelet glycoprotein receptors have been associated with myocardial injury and dysfunction after cardiac and noncardiac operations in adults.

The sequencing of the human genome and the success of the International HapMap Project, along with technological advances in high-throughput sequencing and genome scanning array technologies, have enabled the detailed interrogation of human genomic variability. Applying these techniques to the field of pediatric cardiac surgery will improve our understanding of how genetic variation affects homeostatic mechanisms subjected to perioperative stressors and how these mechanisms determine clinical outcome. The ultimate goal of such an endeavor is to identify targets for personalized intervention to lower the risk of adverse outcome.

Genetic Determinants of Variation in Outcomes in Tetralogy of Fallot

Tetralogy of Fallot is a condition with relatively homogenous anatomy but known variability in genetic pathogenesis. A multi-institutional prospective study of infants with tetralogy of Fallot might help elucidate the genetic determinants of outcome in this patient population. Such a study would require DNA banking and careful phenotyping of the patients, along with detailed recording of preoperative, intraoperative, and postoperative course. Periodic standardized evaluation, including growth parameters, neurodevelopmental testing, and imaging would be performed. Evaluation of genetic variation could be accomplished with multiple strategies, and having banked DNA would allow analyses with new techniques in the future. One strategy could use a candidate gene approach based on a priori hypotheses. Starting points might include polymorphisms in apolipoprotein E or mediators of inflammatory, coagulation, oxidative stress, and neuroendocrine stress, as well as transcription factors with known causal association with tetralogy of Fallot such as NKX2.5 and GATA4. In addition, a genome-wide approach to identifying genetic polymorphisms associated with specified outcomes might identify novel genetic pathways.

The conduct of such studies requires dedicated resources such as a repository for biological specimens and a clinical registry. Efficient conduct of studies across multiple populations requires stable support for these resources, as well as scalability and flexibility of their platforms.

Repository

A repository to collect, catalog, and store DNA, serum, tissue, and mitochondrial DNA for myocardial energetics studies should be a priority for the congenital cardiac community. Specimen collection should be an adjunct to all PHN-sponsored studies, either as part of the specific aims or to allow prospective or retrospective ancillary studies. The
current PHN repository, which houses serum and whole blood for DNA, could be expanded to accomplish these goals. Having DNA linked with a well-phenotyped cohort will be an invaluable resource for cardiovascular researchers.

Registry
Obtaining systematic, prospective data on as many children with CHD as possible is another important goal. The purpose of such an effort would be to describe outcomes of well-characterized groups of children over time. Establishing well-phenotyped cohorts with companion banked biospecimens would provide mechanistic insights, generate hypotheses, and provide readily accessible subjects for trial participation. Children with complex CHD are the group with the highest morbidity and mortality and for which the least evidence-based care exists. Therefore, initiating a registry to recruit these children at the time of diagnosis and follow them up longitudinally is recommended. A registry based on a flexible platform with common data collection forms and a uniform data dictionary that could be used in a variety of settings (eg, different clinical trials and studies, screening and recruitment for studies, and routine clinical care) would greatly enhance the work of the PHN.

NHLBI has recently initiated the Pediatric Cardiac Genomics Consortium.38 This consortium is a cooperative investigative group that will conduct clinical and translational research on the genetic causes of CHD and genetic modifiers of outcome in individuals with CHD. It will interact with the PHN to encourage translation of results from basic science to clinical research and to provide clinical input on pressing needs for basic research.

Challenge: Technological Advances
Advances in imaging, clinical monitoring, medical devices, and bioinformatics have favorably affected outcomes in CHD. This working group specifically addressed medical devices and bioinformatics because of barriers hindering diffusion of these medical advances into pediatric cardiology, including limited incentives for industry and regulatory and ethical issues.39 To overcome these barriers, leaders in the field must advocate for the evaluation and adaptation of these technologies to the setting of pediatric cardiac surgical care.

Medical Devices
Surgical devices designed specifically for children are available in Europe but have not been introduced in the United States in part because of the limited number of patients available for study at any one center and the requirement for maintaining a longitudinal database on outcomes in the patients. In addition, exciting new technologies now used in adults have not been adapted for pediatric use. A partnership between participating clinical centers of the PHN, the Food and Drug Administration, and industry may provide a unique platform for the design and conduct of phase I/II trials to evaluate the safety and efficacy of medical devices for use in pediatric cardiac patients.

The biodegradable annuloplasty ring is an example of a device used in Europe but not available in the United States. A traditional annuloplasty ring in pediatric patients has both advantages and disadvantages. Although an annuloplasty ring produces a more durable result, in a growing child, it may cause mitral stenosis as the child grows. The Kalangos-Bioring (Bioring SA, Lonay, Switzerland) is a partial ring made of 1,4-polydioxanone that is implanted directly into the annulus. After implantation, it degrades by hydrolysis and induces a subendocardial fibrous reaction for stable remodeling of the annulus.40 The published experience of its use in Europe involves 40 patients; the youngest is 5 years of age. Compared with the traditional rigid annuloplasty ring, the biodegradable ring resulted in significantly lower mitral valve gradients during the first year after implantation and reduced cross-clamp and bypass times during the operation.41

Bioinformatics
The creation of a bioinformatics infrastructure would allow all PHN constituencies to share data and knowledge. Such a collaborative information network could be modeled on the National Cancer Institute’s Cancer Biomedical Informatics Grid.42 As an interoperable biomedical informatics infrastructure, the informatics grid has been constructed to deal with 3 important areas: (1) the management and manipulation of large volumes of data (eg, output from genomics/proteomics research); (2) the management, analysis, and dissemination of clinical and public health information (eg, electronic medical records, registries); and (3) the ability to bridge the informatics worlds of basic science and clinical science to facilitate the sharing of data along the continuum of bench to bedside.42 The informatics grid investigators have developed standardized data, management, and analysis tools, and the infrastructure of the informatics grid has been built through the use of open-access, open-source, and federation principles, allowing anyone to use, modify, and help develop the various components of the system.

These and similar tools can be leveraged to create an integrated network of data and tools for the pediatric cardiac community, which would serve as a platform for sharing and analysis of clinical, genetic, and imaging data by virtually linking and accommodating multiple data sources or users. Examples of how such a platform might be used include analysis of phenotypic data in a clinical database with genomic data from a specimen repository or compilation of MRI data from multiple sources to help answer specific research questions.

Such an effort would be greatly improved by a common language. The development of uniform nomenclature and definitions, common database elements, meta-data (data providing information about the content of a certain item), and standardized assessment tools and the ability to capture continuous high-fidelity perioperative hemodynamic monitoring data would enhance the efficiency and efficacy of data collection and sharing. The development of a uniform nomenclature is currently underway, as is an effort to unify the various complexity adjustment methods.43 Standardization of various assessment tools such as for perioperative data collection, echocardiography, cardiac MRI, brain MRI,44 and neurodevelopment is also required for effective synergy between users.

Challenge: Practice Variation and Quality Improvement
Practice variation in the perioperative care of neonates with CHD is significant, driven by physician preference, experi-
ence, and uncertainty resulting from the lack of sound evidence. Most practices in the perioperative period have not been rigorously studied in sufficiently powered randomized controlled trials. This variation in practice constitutes a natural although uncontrolled experiment in which the impact of various practices on outcome can be investigated. New hypotheses can be generated on the basis of identified practices that potentially discriminate between outcomes. In general, practice variation can and should be leveraged to share unique experiences and observations that are not amenable to trial analysis and, in cases when trial methodology can be applied, to achieve a more solid evidence base so that variation can be reduced and outcomes improved.

Successful analysis of practice variation requires a well-phenotyped and relatively homogenous patient population and well-defined and uniformly measured outcomes. The PHN SVR trial cohort provides a unique opportunity to evaluate practice variation across the continuum of perioperative care. The SVR trial data set includes hundreds of measures at multiple time points for the 555 randomized patients. Examples of questions that can be explored, if not answered definitively, include determining the most effective mode of perfusion (RCP versus DHCA), assessing the relationship between a number of perioperative interventions and outcomes, and determining the influence of socioeconomic status on outcomes. In addition, aprotinin was taken off the market partway through the SVR trial, so the effect of this change on perioperative and postoperative management could be evaluated.

Use of Large Data Sets
A number of large clinical registries and administrative data sets can currently be leveraged to evaluate practice variation and its impact on outcome. These include the Society of Thoracic Surgeons' National Congenital Database, the Pediatric Health Information System database, and the Healthcare Cost and Utilization Project’s Kids’ Inpatient Database and Nationwide Inpatient Sample. For example, the Pediatric Health Information System could be used to evaluate the safety profile of aprotinin in pediatric cardiac patients using a case control design. An important limitation of administrative data sets is their limited clinical information. A potential means of overcoming some of these limitations is to combine a clinical registry with an administrative data set through the use of various data-matching algorithms. For example, the Society of Thoracic Surgeons surgical database could be matched with the Pediatric Health Information System database to evaluate the clinical impact of various perioperative practices.

Translating an understanding of practice variation into improved patient outcomes requires a quality improvement initiative. The working group endorsed the idea of a collaborative quality initiative within the PHN. An essential component of a quality improvement program is a patient database or registry that incorporates relevant end points. Judging from the successful models of others, a quality improvement program involves evaluating information about current practices, identifying areas for improvement, developing and implementing change initiatives, measuring the effects of those initiatives, and finally maintaining those initiatives that bring about improved outcomes. Aspects of a quality improvement program might include feedback on institutional practices and outcomes, feedback on how institutional results compare with the network as a whole, identification of quality indicators and best practices, training in quality improvement techniques, site visits of high performers, dissemination of results and knowledge gained, and continuous measurement and evaluation of results.

Unmet Needs and Remaining Challenges in Pediatric Cardiac Surgery
As the success of initial palliative and corrective procedures for complex CHD has increased, new and unexpected challenges have arisen that require innovative strategies to overcome (the Table). The PHN infrastructure and resources, including informatics network, analysis of practice variation, and clinical trials design and analysis expertise, may serve an important facilitative role in solution development.

Conclusions
The PHN SVR trial demonstrated that certain surgical questions are amenable to rigorous randomized controlled clinical trials. The completion of this trial will raise the standard for the application of evidence-based practice to the care of patients with CHD during the perioperative period. This
working group identified potential next-step clinical trials and resources that will be necessary to achieve this new standard. Advancement in the field will require an improved understanding of the short- and long-term sequelae of the perioperative experience, a deeper appreciation of how genomic variation and practice variation affect outcome, and the harnessing of technological innovation to service these goals. The perioperative care of the patient with CHD remains an important challenge in medicine; the ideas of this working group will help navigate the way forward.

Appendix

Additional Working Group Members

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Invited Speakers

Kenneth Gueret, PhD, National Cancer Institute; David Bull, MD, University of Utah Health Sciences Center; Patrick McQuillen, MD, University of California, San Francisco Medical Center; Richard Prager, MD, University of Michigan; Simon Paterson, MD, Dow Neurobiology Laboratories; Aoy Tomita-Mitchell, MD, PhD, Medical College of Wisconsin; Hector Wong, MD, Cincinnati Children’s Hospital Medical Center; and Ajit Yoganathan, PhD, Georgia Institute of Technology.

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Table. Challenges in Pediatric Cardiac Surgery

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<th>Challenge</th>
<th>MAPCA indicates major aortopulmonary collateral arteries.</th>
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<td>Right ventricular dysfunction late after surgery (tetralogy of Fallot)</td>
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<td>Ascending aortic enlargement in adults with conotruncal anomalies</td>
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<td>Extreme prematurity and cardiopulmonary bypass</td>
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References


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