Improving neurologic and quality-of-life outcomes in children with congenital heart disease: Past, present, and future

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They say that time changes things, but you actually have to change them yourself (Andy Warhol).

Prostaglandin and Echocardiography

That's what started this whole journey. Before the end of the 1970s, most neonates with critical congenital heart disease (CHD) did not survive if their pulmonary or systemic blood flow was dependent on a patent ductus arteriosus. Even in the rare neonate who was lucky enough to have spontaneous patency of the ductus, making a complete diagnosis to plan cardiac surgery required catheterization; 30 years ago cardiac catheterization was associated with significant morbidity, especially in a fragile neonate. It's no wonder surgical mortality was so high in those days. Even though the technical aspects of cardiac surgery could be applied to small babies, the status of the infant entering the operating room was tenuous, and the infant not infrequently had an incomplete diagnosis.

Enter bedside noninvasive diagnostic capabilities and the availability of medical support to stabilize the infant. Mechanical ventilation was being applied to smaller and smaller infants, hemodynamic monitoring was improving, and the new subspecialty of cardiac intensive care allowed for increasingly stable babies to survive palliative and reparative procedures. Improvements in surgical technique and cardiopulmonary bypass followed soon thereafter. Intraoperative echocardiography increased the likelihood of leaving the operating room with a better understanding of the physiology of the neonate and status of the repair.

For those of us in the practice of pediatric cardiology, this was an exciting time indeed. Survival, even for infants with the most complex lesions, was now *expected*. Cardiologists and intensivists painted a very different prognosis for families than we had even 10 years earlier. However, with these successes came new realizations. As we began to observe these outpatients in larger numbers, we recognized that there was an unexpectedly high prevalence of psychosocial, neurologic, developmental, and psychiatric disabilities in the survivors as they entered and proceeded through formal education. Gross and fine motor delays, learning disabilities, inattention, hyperactivity, internalizing and externalizing behaviors, and speech and language difficulties have all been reported with disturbingly high frequency, approaching 40% to 50% in some subgroups.¹ The neurodevelopmental burden of disease is, for many children and their families, much more significant than the daily impact of their CHD.^{E1} (See E-References on line.) Many families of teenagers with complex CHD and significant learning or behavioral problems openly ask me why they were not informed of these potential problems when their children were born. It is of little solace that I tell them that when their child was born in the late 1980s and early 1990s, there were simply not enough school-age survivors to know the true impact of CHD and its management on longer term quality of life. Fortunately, children and their parents began to participate in longitudinal clinical research efforts so that we might gain improved understanding of the types and frequency of neurodevelopmental dysfunction and begin to understand the mechanism(s) of injury.

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Partnership and Equipoise

In this issue, the investigators at Children's Hospital Boston present another in a series of important investigations aimed at improving our understanding of the mechanisms of central nervous system injury in the operating room and proposing changes in management to improve the longer term outlook for our current patients.^{2,3} At the outset, Newburger (cardiology), Jonas (cardiac surgery), Bellinger (psychology), Wypij (biostatistics), and their many colleagues understood the value in the multidisciplinary design of clinical investigations. I was fortunate as a junior physician to be mentored by that group. *Partnership* extended from study design through implementation in the intensive care unit, getting "buy-in" from colleagues in medicine, surgery, anesthesia, and nursing, and most importantly, the families of our patients. We believed then, as now, that clinical investigation of long-term outcomes was a moral imperative and all needed to participate as partners in the challenge, from many disciplines both inside and outside of pediatric cardiology and surgery. Whereas getting many investigators (frequently seasoned investigators with long research track records) to agree on the important questions, the patient population to study, the financial realities of clinical studies, and even the order of authors on manuscripts was "challenging," *equipoise* was perhaps the hardest of all hurdles to overcome. In our field, it is natural to "know" (or be expected to know) the "correct" approach to a procedure, the "right" diagnosis: the "truth." How can a surgeon with so much on the line be expected to "flip a coin" to decide what bypass strategy to use, what surgical technique to use? How could we convince parents of critically ill neonates to sign a consent form allowing us to be—by design—*random* in our decision making?^{E2} How could we convince our colleagues who referred patients to us to allow their patients to enter a clinical trial? These were difficult problems in theory, but the leadership in the cardiovascular program provided by Dr Aldo Castañeda and Dr James Lock continued to foster an approach that this was clearly the best way in which the field could move forward and improve results for the next generation. Multidisciplinary study groups were encouraged and indeed became the model of clinical investigation of long-term outcomes for our patients.

The knowledge gained from the randomized trials in Boston have included investigations of the use and duration of deep hypothermic circulatory arrest,^{4,5,E6-E11} pH management,^{6,E12} and, in the current issue, follow-up and further analysis on the effect of hematocrit management during cardiopulmonary bypass.^{2,3,E13} Much has been learned from these trials that has affected our current approaches to cardiopulmonary bypass and perioperative management. In addition to the lessons learned from the important trials in Boston, a subtle "culture change" has occurred

in our field. New changes in technique are more frequently subjected to critical review and implemented as clinical trials rather than immediately adopted as "better" or "proven." Practice change by anecdote, seniority, or by comparing new techniques to historical controls is no longer a viable, acceptable strategy.^{E14} Additional randomized clinical trials of intraoperative and perioperative management have recently been published^{E15,E16} and are currently underway, including multicenter trials supported by the Pediatric Heart Network (www.pediatricheartnetwork.org/currentstudies.asp, accessed 2007).

Prospective and Evidence-based Studies

In addition to the randomized studies in Boston, a number of cohorts are currently being evaluated prospectively with protocol-driven follow-up to learn more about the impact of factors outside the operating room that affect long-term neurodevelopmental outcomes. Large cohorts of patients with heterogeneous CHD are currently being prospectively followed up at The Children's Hospital of Philadelphia^{7,E17-E20} as well as at Montreal Children's Hospital^{8,E21-E28} and the University Hospital in Aachen, Germany.^{9,E29-35} Additional prospective and cross-sectional reports are increasingly prevalent in the literature.^{E36-E42} All of the current evidence points to the fact that modifications of technique in the operating room, although important, contribute but a small fraction to the variability of longer term outcomes in the decades that follow neonatal cardiac intervention. Instead, nonmodifiable factors such as gestational age, birth weight, genetic syndromes and polymorphisms, maternal education, and socioeconomic status have been consistently and significantly implicated as major contributors to long-term outcome.^{E43} Therefore, prospective studies must continue to define the impact of modifiable risk factors: *how* we operate, *when* we operate, and importantly, *how* we manage the patient in the *intensive care unit*. During a typical hospitalization for neonatal heart surgery, only a small fraction of the total length of stay is spent in the operating room, where a disproportionate (though very important) amount of clinical investigation has taken place. Resources and clinical investigations need also to study management patterns in the intensive care unit. Changes in management must be accompanied by investigation into their short- and long-term impact to establish an evidence base to design future prospective follow-up studies and randomized treatment clinical trials. Just a few examples of practice patterns that have not been adequately studied for their impact on longer term neurodevelopment include timing of surgery in critical lesions, "routine" delayed sternal closure,^{E44-E47} management of hyperglycemia,^{E48,E49} temperature control,^{E50-E52} nutrition,^{E53} and the impact of mechanical ventilation/hyperventilation^{E54} on longer term outcomes. Some are likely to be important, and it is time to study factors in the intensive care unit as

rigorously as we have studied factors in the operating room. We need to be more critical of our current strategies as being “right.” We should model our trials and clinical investigations on the approach taken by the Boston group for nearly 20 years, to have equipoise regarding our current strategies, study them rigorously, in a multidisciplinary, multicenter, and importantly, long-term fashion. We may find that our *practices and established techniques* may be all wrong.

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