Editorial

When is early septal myectomy in children with hypertrophic cardiomyopathy justified?

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Introduction

Pediatric cardiomyopathy is a debilitating disease that leads to pump failure and sudden death; in fact, it is the leading cause of heart failure in children (1). Cardiomyopathy and heart failure in infants and children remain serious population health crises for children and their families and confer a great cost burden on society (2-5). In the United States, the estimated annual incidence of congenital cardiovascular malformations or cardiomyopathy in infants, children, and adolescents less than 19 years old is between 12,000 and 35,000 (6).

How then should parents proceed when faced with their infant's or child's suffering and potential death from symptomatic refractory hypertrophic cardiomyopathy (HCM)?

In 1958, Teare reported a seminal series of eight children with HCM, of whom seven died of sudden presumed cardiac death at a young age (7). Two years later, Goodwin *et al.* described surgical management targeted to the hypertrophied intraventricular septum of the heart (8). More recently, Schleihauf *et al.* published a retrospective (1978 to 2015), single-center study in Germany that evaluated the long-term outcomes of septal myectomy for 23 infants and children with obstructive HCM (defined as an echocardiographically-derived peak instantaneous gradient across the ventricular outflow tract of more than 50 mmHg, a mean instantaneous gradient of more than 30 mmHg, or a catheterization-derived peak-to-peak gradient of more than 30 mmHg) (9). Of the 23 children and adolescents in that series, 11 were between 1 and 18 years old at the time of surgery. Notably, the complication rate was 25% (3/12) in younger children and 64% (7/11) in the older children, for a combined complication rate of 43%. Arrhythmias were detected in 17% (2/12) of younger children and in 27% (3/11) of older children. Two of the 11 younger children required a repeat myectomy. Others have also reported increased surgical risks: transaortic surgical myectomy in infants and children is associated with complications such as aortic or mitral valve injury, new-onset heart block, re-operations, and early and late mortality (10,11). Despite these remarkably high complication and reoperation rates, Schleihauf *et al.* recommend early and aggressive surgery for these infants, children, and adolescents (9).

Conducting trials in children with cardiomyopathy

Schleihauf *et al.* should be congratulated on their study, but there are limitations here that warrant consideration. One major challenge to conducting trials in infants,

children, and adolescents with cardiomyopathy, and in extrapolating from this Schleihauf *et al.* study, is the low number of eligible patients: the incidence of HCM is only 0.47/100,000 children (12). The number of young children in the United States requiring surgical septal myectomy for HCM is small. Furthermore, the retrospective nature and the small sample size of the study by Schleihauf *et al.* limits its generalizability to other patients with HCM as we don't know if confounders are coming into play.

A second challenge of these studies is choosing appropriate endpoints. Methods for selecting and interpreting study endpoints in evaluating policy and service interventions remain contested (13). Several surrogate endpoints, such as serum biomarker concentrations, imaging studies, and disease severity, are commonly used to assess the effects of interventions. Although these surrogate endpoints may be used for risk stratification, many have not been validated as surrogates for hard clinical endpoints, such as death or cardiac transplantation.

A third challenge, illustrated by Schleihauf *et al.*, is that HCM is often studied as a single disease, irrespective of its cause or co-morbidities, which could confound and undermine its statistical inferences. Studies of the United States National Heart, Lung, and Blood Institute-funded Pediatric Cardiomyopathy Registry (14,15) have reported that among pediatric patients with HCM presenting in infancy, the prognosis for those with inborn errors of metabolism or with mixed hypertrophic and dilated or restrictive cardiomyopathy is worse than those with HCM from other causes (16). But when we compile observational study on top of observational study, we become more likely to achieve statistical significance without improving clinical significance. In other words, very small differences are real, but that doesn't necessarily mean those differences are meaningful.

A fourth limitation is the limited length of post-myectomy follow-up. The overall effectiveness of a surgical procedure should be determined by assessing the overall quality of life of the child undergoing the surgical procedure and their family over a lifetime, as determined by both the clinical efficacy of the surgery and the complications and late effects. With only limited follow-up of patients in this series the overall clinical effectiveness of septal myectomy in infants and children with HCM simply cannot be determined based on available data.

Surgical outcomes

Surgery in many infants, children, and adolescents leads to long-term morbidity, likely secondary to myocardial fibrosis and left ventricular dysfunction. In children with idiopathic cardiomyopathy after 1 year of age, the annual mortality rate is 1%, which is similar to the population-based studies in adults with HCM (17). Children with Noonan syndrome are more likely to present in the first 6 months of life and have a higher risk of death than that for children with HCM from different causes (18). Although Schleihauf *et al.* did not report the prevalence of heart failure or age in their patients with Noonan syndrome, the median age for all 12 infants was 8 months, and 9 of the 12 had Ross Heart Failure Class III/IV (9). The mortality was highest for children with Noonan syndrome who presented with HCM before they were 6 months old as compared to presenting after 6 months (1-year survival, 64% *vs.* 5-year survival 96%). Also, the children with heart failure had poorer survival than those who did not (34% *vs.* 90%, P<0.001). These high-risk patients may be the best candidates for septal myectomy, especially in those with medically refractory heart failure early in life (19).

Schleihauf *et al.* found that early surgical mortality was 4% (1/23) and late mortality was 9% (2/22). The authors report a long-term reduction in the ventricular outflow tract gradient, as well as an associated improvement in clinical status. However, the authors acknowledge that about a third of their patients had persistent systolic anterior motion of the mitral valve and moderate mitral regurgitation, which greatly undermined the child's wellness, growth and development and exercise tolerance. Related, in a large study of adults from the Nationwide Inpatient Sample database, the overall mortality associated with ventricular septal myectomy was 5.9%, which increased to 8.7%, if the patients had a post-procedural complete heart block that required the insertion of a pacemaker (20).

Delivering reliable surgical care to infants, children, and adolescents with intractable cardiomyopathy is complex and organizationally challenging, and expensive (21). Surgical performance and outcomes depend on complex human factors—the individual, technical, and organizational factors and the complicated interactions among them (22). The organizational learning characteristics rely on complex team-based care, the acquisition and maintenance of individual technical and non-technical skills, the applications and consequences of technology, the impact of the work culture, and the reliability and success of team performance (23,24). Several factors have been linked to poor surgical outcomes, including low institutional and surgeon- or operator-specific volumes, case complexity,

team coordination and collaboration, communication across elements of care, old technology, human-machine interfaces, and systems failures (25). Child safety and team resilience in these organizations can ultimately be understood as specific characteristics of the system—the sum of all its parts plus its design, relationships, and interactions (26). The need for heightened situational awareness, robust communication practices and an emphasis on a culture that values speaking up about the potential for failure at any stage should be on the minds of every team member in addressing the highly variable outcomes of surgical septal myectomies (23).

A more reliable dynamic risk management system is needed in treating these pediatric patients with HCM, and in guiding their parents about how best to support their children's growth and development, including more real-world, and practical consensus guidelines on definitions, management, and how best to counsel parents (27). It is imperative to use these guidelines widely and consistently by all stakeholders, not just the providers, but also insurers and policy makers.

An increasing number of studies have also reported that undergoing anesthesia before the age of three years, and certainly before the age of one year, is associated with a range of short- and long-term neurologic developmental problems. A recent United States Food and Drug Administration review of anesthesia in infants resulted in new warnings advising that prolonged or repeated exposure to general anesthetics may affect neurodevelopment in children and should be avoided unless it is absolutely necessary (28,29). Most, but not all, of the large population-based studies find evidence for associations between surgery in early childhood and slightly worse subsequent academic achievement or increased risk for later diagnosis of a behavioral disability (30). Similar concerns exist about the long-term consequences and late effects of surgical ventricular resections performed early in postnatal life.

Improving quality outcomes for infants and children with HCM

Improving the quality outcomes in infants and children is challenged by a system that lacks a fundamental infrastructure for children's healthcare in general and for pediatric cardiomyopathy in particular. In our opinion, Schleihauf *et al.* should have also included secondary endpoints, such as patient-reported quality-of-life scores because these outcomes are increasingly central to effective and shared decision making with parents (31). The process of harvesting the learning from the data on how best to treat children with cardiovascular illnesses is iterative and typically incremental, constantly being infused by real work experience and hard-earned lessons by clinicians providing clinical care (32). The willingness to learn from process and outcome about near-misses and failures is the cornerstone for highly reliable outcomes (33). Developing sustainable learning towards improved outcomes in pediatric cardiomyopathy will require using the applied sciences of health services research and implementation science in order to translate clinical practice lessons and learnings that will challenge and change entrenched clinical practices.

Next steps: we need better studies and more effective learning

Surgical intervention on an infant's ventricle always has many long-term adverse effects, such as dyskinesia, arrhythmias, and the potential for retarded growth. We believe that the deleterious long-term effects of septal myectomy in infants with HCM-related refractory symptomatic cardiomyopathy, combined with the well-documented danger of early age anesthetic exposure, does not warrant early surgery in a generalized way. High-risk children with HCM and heart failure appear to be the best candidates for septal myectomy, especially those with medically refractory heart failure early in life.

If we want fresh knowledge, a big randomized controlled, or pragmatic adaptive, multi-center study is needed to evaluate the long-term physical, emotional, and developmental outcomes in HCM and to assess the short- and long-term benefits of surgical myectomy. Public reporting of outcomes will be critical to evaluate the balance between clinical efficacy and complications/late effects on this type of pediatric cardiac surgery (34).

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Footnote

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