Hypoplastic left heart syndrome: How to improve late survival and quality of life

Robert D. B. Jaquiss, MD

From the Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University School of Medicine, Durham, NC.

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Address for reprints: Robert D. B. Jaquiss, MD, Duke University School of Medicine, Cardiothoracic Surgery, DUMC 3474, Durham, NC 27710 (E-mail: robert.jaquiss@duke.edu).

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For those who care for children with congenital heart disease, hypoplastic left heart syndrome is at once the most rewarding and the most frustrating anomaly to manage. The reward is obvious in that this common (1 in 960 births in the United States) and once uniformly lethal lesion can now be effectively palliated in the majority of cases, and usually for many years. The frustration arises in that the effectiveness of the palliation is limited in both scope and durability, and that each advance seems to provoke new questions and unmask new problems. The pioneers and investigators working in this arena share the twin goals of improving both the quantity of life, expressed as long-term survival, and the quality of life, a more elusive index of success.

The sine qua non of long-term survival is short-term survival, and it is here that the greatest strides have been made, beginning with the development of the Norwood operation, consisting of arch reconstruction, atrial septectomy, and pulmonary blood flow provided by a systemic artery-to-pulmonary artery shunt (modified Blalock-Taussig shunt).¹ A modification of surgical technique by the reintroduction of the right ventricular-to-pulmonary artery shunt (RVPAS)² and the introduction of interstage surveillance with a “home-monitoring” program³ were associated with major improvements in short-term survival in single-center reports. The former was then rigorously evaluated in a randomized study, the Single Ventricle Reconstruction (SVR) Trial, comparing the 2 versions of the Norwood procedure, modified Blalock-Taussig shunt and RVPAS, with initial focus on the end point of transplant-free survival.⁴ At 1 year, there was a statistically significant advantage of approximately 10% in favor of the RVPAS. By 5 years, however, the advantage of RVPAS relative to the modified Blalock-Taussig shunt was less than 5% and no longer statistically significant.⁵ Certain disadvantages of the RVPAS also emerged during the longer term, including more pulmonary artery distortion requiring reintervention and worse right ventricular systolic function, usually attributed to the right

Robert D. B. Jaquiss, MD

Central Message

The initial hurdle of early survival in HLHS has been overcome. Late survival and acceptable quality of life remain challenging.

See Article page 1440.

See Editorial Commentary page 1453.

ventriculotomy.^{5,6} Conversely, a recent retrospective propensity-matched study including Norwood operations performed between 2005 and 2014 demonstrated prolonged advantage of the RVPAS in terms of survival and possibly of RV function.⁷ An explanation for the discrepant verdicts on the RVPAS relates to the eras of the 2 studies: enrollment of patients in the SVR Trial ended in July 2008. Since that time, numerous modifications of the RVPAS have been proposed. These include the use of a reinforced conduit,⁸ rightward placement of the shunt relative to the neo-aorta, and the “dunk” technique for the proximal anastomoses.^{9,10} These changes were designed to minimize distortion of the pulmonary arteries and reduce injury to the right ventricle. Although the impacts of these iterations are only now being formally assessed, at a minimum it may be asserted that the RVPAS is performed far differently, and almost certainly better, in 2015 than in 2008. Other important improvements with benefit to patients receiving either version of the operation include the widespread application of interstage monitoring and optimized timing of the second-stage operation.¹¹

Despite the many advances in surgical techniques, perioperative care, and operative timing, patient attrition

has not been eliminated, with only 70% of patients expected to reach adulthood.¹² Early in the staging process, death or concept failure resulting in referral for transplant are most commonly related to ventricular dysfunction, with or without important tricuspid regurgitation. It is typically several years before the appearance of “failing Fontan” physiology, marked by protein-losing enteropathy, liver dysfunction, renal dysfunction, and, rarely, plastic bronchitis. Even for the many patients who avoid these sequelae in the first decade or so of life, it is unlikely that the Fontan circulation will be durable for the 8 decades that biventricular circulation is expected to provide. Indeed, it has been suggested that the Fontan circulation should be thought of as a bridge to transplant. With that in mind, the staging sequence should be conducted so as to optimize and preserve transplant candidacy, particularly because no mechanical circulatory support modality has yet been demonstrated to be a reliable bridge for patients with univentricular physiology, much less a reasonable option for destination therapy. For now at least, the only solution is transplant. In this context, it is important to minimize allosensitization, currently present in approximately 40% of post-Norwood transplant candidates.¹³ This has been partially accomplished by treating allograft material used in the first-stage operation with dilute glutaraldehyde¹⁴ but is perhaps more effectively achieved by avoidance of such material altogether. Likewise, “bloodless” conduct of subsequent staging operations is both intrinsically desirable, and helpful for future transplant candidacy. Another important pretransplant morbidity to avoid is venous thromboembolism, which could irreversibly injure the pulmonary vascular bed. Unfortunately, possibly because the Fontan circuit is inherently thrombogenic, effective prophylaxis has proved difficult.¹⁵ Perhaps the most difficult long-term issue is the seemingly inexorable declines in renal and, more particularly, hepatic function, which might necessitate multiorgan transplantation or preclude transplant candidacy altogether.¹⁶

As survival has improved, there has been disappointingly little improvement in neurologic outcomes for post-Norwood patients. Two interim evaluations of the SVR cohort, at 14 months and 3 years, found neurodevelopmental performance to be well below population norms.^{17,18} Not surprisingly, there was no advantage of either shunt relative to the other in either analysis, and no easily modifiable treatment strategies appeared as risk factors for worse outcome. As sophisticated preoperative neuroimaging of patients has become routine, it is now clear that children with complex congenital heart disease have a significant incidence of acquired or developmental abnormalities of the brain, including hemorrhages of various size, white matter injury (frequently termed “periventricular leukomalacia”), and findings simply

consistent with immaturity of as much as 4 weeks relative to a cohort without congenital heart disease.¹⁹ These findings have been termed “the encephalopathy of congenital heart disease.”²⁰ The potential implications for the management of children with hypoplastic left heart syndrome are several. In the setting of recent intracranial hemorrhage, delay of the first -stage operation, with its mandatory intense anticoagulation and associated coagulopathy, seems sensible. This may be facilitated by temporary bilateral pulmonary arterial banding. In a similar vein, it might seem reasonable to delay surgery in the setting of a normal but simply “immature” brain. Despite that apparently logical assumption, however, a recent study suggested that a delay of even a few days was associated with a higher risk of periventricular leukomalacia.²¹ This question of timing of surgery is particularly important, both because the concept of “neuroprotection” has thus far been fairly unrewarding²² and because surgical scheduling is perhaps the most easily controlled of all perioperative variables. The avoidance of bypass in the neonatal period altogether, by means of the “hybrid sequence,” has been suggested as a solution, but proof of this hypothesis is not yet available.

In summary, remarkable progress has been made in the treatment of this common and formerly lethal condition, particularly with regard to improvement in early survival. As early survival is now the rule rather than the exception, the stage is set for improved long-term survival. This must be accomplished with attention to details that will also optimize the quality of life and functional status of survivors, with particular focus on neurologic, pulmonary, and hepatic function to prevent or manage long-term complications and preserve transplant candidacy.

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