Single Ventricle Reconstruction Trial: A Work in Progress

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Hypoplastic left heart syndrome, which occurs in 1 per 5,000 live births, refers to a family of cardiac defects which are characterized by hypoplasia of the structures comprising the left side of the circulation, including the mitral and aortic valves, the left atrium and left ventricle, and the aorta. Infants with this syndrome typically undergo a 3 stage surgical palliation. Without this surgery, the defect is lethal. Since the report of the first Norwood procedure for hypoplastic left heart syndrome by Dr. William Norwood in 1981, results from treatment of hypoplastic left heart syndrome have improved considerably.\(^1\) In a large single center report, operative mortality associated with the first stage procedure was reduced from 59% to 19% between 1990 and 2001.\(^2\) Nonetheless, the complete palliative sequence entails 3 surgeries and entails considerable inter-stage mortality as well, so the overall survival for patients with hypoplastic left heart syndrome remains poor.

In 2003, a major modification of the classic Norwood Stage 1 procedure was introduced, substituting a shunt from the right ventricle to the pulmonary artery (RVPA), for the traditional modified Blalock-Taussig shunt (MBT) which carries blood from the brachiocephalic artery to the pulmonary artery.\(^3\) There are several theoretical advantages to the RVPA shunt, stemming from the absence of diastolic blood flow from the systemic circulation to the pulmonary circulation. These include increased coronary flow; enhanced post-operative stability; and reduced interstage mortality. As potential disadvantages, the RVPA shunt entails creation of a right ventriculotomy; creates free pulmonary insufficiency; and may be inferior to the MBT shunt in promoting pulmonary artery growth due to the altered pulmonary blood flow patterns.\(^4\)

Against this backdrop, the NIH funded a landmark randomized surgical trial, the Single Ventricle Reconstruction Trial, which was conducted via the Pediatric Heart Network, enrolling 549 infants with Hypoplastic left heart syndrome across 15 North American Centers.\(^5\) In this
study, the RVPA shunt and MBT shunt were compared. The primary study outcome was the rate of death or cardiac transplantation at 12 months, compared between the two shunt groups. The results of this trial, which were published in 2010, showed that the RVPA shunt offered greater survival at 12 months (74% for RVPA vs. 64% for MBT).\textsuperscript{5}

Interestingly, when transplant-free survival was compared between groups using all available follow-up data rather than truncating at 12 months, the survival advantage of the RVPA shunt was no longer seen, complicating interpretation of the study results.

Over the following years, a number of secondary analyses from the Single Ventricle Reconstruction Trial have been published, illuminating additional aspects of a highly complex disease and treatment.\textsuperscript{6-11} Importantly, a detailed analysis of mortality from the initial trial demonstrated that 54% of deaths occurred during the initial operation and associated hospital stay, while 33% of deaths occurred after hospital discharge, while awaiting the second stage operation (interstage mortality). The second stage operation and subsequent follow-up accounted for the remaining 14% of deaths.\textsuperscript{9} The hospital mortality rate during the Stage 1 operation was 16% and was not related to the shunt type.\textsuperscript{10} However, interstage mortality between Stage 1 and 2 was 6% for the RVPA shunt, and 18% for the MBT group, for an odds ratio of 3.4 for MBT compared to RVPA.\textsuperscript{8} Thus, the major survival advantage of the RVPA shunt was attributable to interstage mortality rather than to procedural mortality. Further analyses demonstrated a complex relationship between anatomic subtype, other innate patient risk factors, and the risk associated with each shunt type. For example, patients who were full-term at surgery and had aortic atresia, were more likely to benefit from the RVPA shunt, while preterm infants with a hypoplastic but patent aortic valve, benefitted from the MBT shunt.\textsuperscript{10} Cumulatively, these secondary analyses greatly enhanced our level of understanding of the
relative benefits of the RVPA shunt as compared to the MBT shunt. They are particularly important in view of the lack of any comparable randomized cohort now or in the foreseeable future that would allow for unbiased comparison of these two surgical approaches.

Newburger and colleagues have taken an important additional step with the current publication of survival outcomes at 3 years in this same cohort. In showing overall equivalence of survival between the RVPA and MBT groups at 3 years, the authors confirm the trend raised in the initial trial publication and demonstrate the complex time-dependence of survival benefit between the surgical approaches. In the early phase, encompassing both surgical mortality and the first interstage interval, the hazard ratio favored the RVPA shunt, while after 12 months, the MBT was favored from both survival and morbidity (as represented by excess interventions). This evolution of risks over time is consistent with the theoretical framework described in the initial study design, whereby the RVPA shunt is associated with more favorable post-operative physiology, but poses problems of pulmonary artery growth and right ventricular function, possibly due to the right ventriculotomy. The results of the current study are also consistent with an alternative hypothesis, that the innate patient risk profile is not altered materially by the choice of shunt. In this explanation, the decrease in right ventricular function described by Newburger and colleagues is a manifestation of survival of a marginal patient cohort with the RVPA shunt, while the MBT shunt did not afford this group the same short-term survival. As this marginal cohort undergoes attrition, persisting equality of the remaining cohort would be expected. Conversely, if the ventriculotomy or other aspects of the RVPA shunt are problematic, that should be evident after additional time elapses, through further divergence of the cohorts. Additional longitudinal studies of this cohort may help elucidate these answers and will be invaluable for these as well as for other reasons.
A cohort of this size, with surgical randomization, is a costly and very precious resource, which should be fully utilized, as is being done with the multiple analyses emerging from the primary trial. At the same time a cautionary note is needed. None of these secondary analyses were part of the primary study power calculation, and there is potential for both over-reaching as well as generation of potentially conflicting results with excessive analysis of the primary study cohort. Much of this can be averted. Study organizers must be mindful of this risk and undertake a comprehensive and thoughtful approach to planning the full spectrum of study analyses at the time of the study design. It would be invaluable to the readers, if that full analysis plan were specified in detail in the initial study design publication. In this manner, the full value of such studies can be realized. In the meantime, for the RVPA shunt, the jury is still out, but the initial advantages of this approach do not appear to be sustained over a 3 year horizon.

Conflict of Interest Disclosures: None.

References:


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