Ancillary revelations of the Single-Ventricle Reconstruction Trial: The less excitement, the better

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The Single-Ventricle Reconstruction Trial published by Ohye and colleagues¹ in 2010 continues to occupy a seminal role in the ongoing debate about whether a modified Blalock-Taussig shunt (mBTS) or a right ventricle-to-pulmonary artery shunt offers a better outcome for patients undergoing a stage I Norwood procedure. Proponents of the mBTS shunt often argue that there is an inherent long-term advantage to avoiding a right ventriculotomy, whereas proponents of the right ventricle-to-pulmonary artery shunt cite inherent disadvantages of having coronary steal during the diastolic runoff in a mBTS. In the randomized Single-Ventricle Reconstruction Trial, Ohye and colleagues¹ concluded that as late as 12 months, transplant-free survival was better with the right ventricle-to-pulmonary artery shunt than with the mBTS, with no significant difference between the groups in transplant-free survival after 12 months. Perhaps more intriguing than their report, however, were the ancillary investigations done during this trial—that of adrenergic receptor (*ADR*) genotype variations of the patients and their associations with secondary adverse events.

In the study presented in this issue of the *Journal*, Ramroop and colleagues² collected buccal swab epithelial cells from the Single-Ventricle Reconstruction Trial population, extracted genomic DNA, and performed genotyping for 4 single-nucleotide polymorphisms in 3 *ADR* genes. Genotyping was also performed for 4 single-nucleotide polymorphisms and 1 insertion-deletion variant in 5 renin-angiotensin-aldosterone signaling (*RAAS*) genes. The primary outcome sought was a composite of any serious adverse event (SAE) during a 14-month follow-up after the stage I Norwood procedure, which included death, transplant, need for extracorporeal membrane oxygenation, cardiopulmonary resuscitation, shunt failure, unplanned reoperations, or necrotizing enterocolitis. They found a lower SAE-free survival during a 14-month follow-up for the 64% of patients that had the wild type *ADRA2A_2790CC* genotype versus the *CT/TT* genotypes. This finding is

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Central Message

Knowing the *ADR* genotype preoperatively may provide insight into subgroups that could benefit from epigenetic or enhanced pharmacologic modulation to minimize adverse events after Norwood palliation.

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significant in that, according to Ramroop and colleagues,² the *ADRA2A_2790CC* genotype is associated with diminished feedback inhibition of norepinephrine and failure to inhibit sympathetic tone. They postulate, convincingly so, that higher sympathetic tone adversely affects systemic output and organ perfusion, resulting in the higher risk of SAEs. Although they do not have hemodynamic data to corroborate their findings, their investigation of the *ADR* genes is very relevant to this population, because one of the primary management strategies for patients after the Norwood procedure is tailored toward achieving a balance between the systemic and pulmonary circulations. Any enhanced chronic sympathetic tone on the systemic side could offset that critical balance and place more stress on the single right ventricle. Knowing the *ADR* genotype before the operation may provide important insight into subgroups that could benefit from epigenetic or enhanced pharmacologic modulation to minimize the risk of SAEs after the stage I Norwood palliation.

References

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