Inflammatory and neurohormonal modulation for congenital heart surgery: The quest continues

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Cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) elicit various biochemical, hemodynamic, and hormonal changes that may contribute to the development of different hemodynamic profiles in children undergoing heart surgery. The proinflammatory environment that exists after CPB and DHCA has been a target for different therapeutic interventions. Hormonal manipulation has been attempted as a means of positively affecting postoperative course. For example, the perioperative administration of corticosteroids is known to cause cellular membrane stabilization, reduction of HLA antigen upregulation, and inhibition of cytokine elaboration. Similarly, thyroid hormone modifies metabolic, immune, and cardiovascular functions and has been administered perioperatively as an optimizing agent to offset its relative reduction after CPB and DHCA.

In this issue of The Journal of Thoracic and Cardiovascular Surgery, Talwar and colleagues report a double-blind, placebo-controlled trial in 100 infants with normal thyroid function. Subjects underwent cardiac surgery and were randomly assigned during a 16-month period into 2 groups (50 in the thyroxine supplementation group and 50 in the placebo group) to determine whether there was an association between oral thyroxine (T4) supplementation and changes in cardiac index (CI), along with other important outcomes. Subjects in the study group received an oral dose of 5 µg/kg of T4 starting 12 hours before surgery and every morning thereafter while in the intensive care unit. Subjects in the study group had higher CI than did the placebo group (CI 0.30 L/min/m² higher; P = .04). This association remained significant in the group versus time interaction analysis (CI 0.53 L/min/m² higher; 95% confidence interval, 0.30-0.76 L/min/m²; P < .0001). Subjects were also stratified into simple and complex categories according to congenital heart lesion and postoperative course for further analysis. Subjects in the complex group who received T4 required shorter duration of mechanical ventilation (study group, 3.85 ± 0.92 days vs placebo, 4.66 ± 1.55 days; P = .001), shorter ICU stay (study group, 6.79 ± 2.26 days vs placebo, 8.30 ± 3.39 days; P = .03), and lower inotropic scores (6.7 less; 95% confidence interval, 2.7-0.7; P < .0001). In addition, Talwar and colleagues found that the interleukin 6 levels were reduced a long as 24 hours in subjects in the study group (P < .001).

It has been well described that early after the initiation of CPB, particularly DHCA, thyroid-stimulating hormone concentration is raised, responding to decreased concentrations of triiodothyronine (T3), and that levels restore during a period of days, beginning with thyroid-stimulating hormone and followed by T3, an entity referred to as “euthyroid sick syndrome.” An actual etiology for these changes has not been precisely described; however, hemodilution, hypothermia, and inflammation have been implicated. As of now, thyroid hormone supplementation remains the mainstay therapy for euthyroid sick syndrome. This study of Talwar and colleagues, like several others, demonstrates that perioperative thyroid hormone supplementation is associated with improved outcomes.

Recent studies have also demonstrated the hemodynamic benefits of oral T3 after CPB. To our knowledge, this is the first study to use oral T4 successfully in this setting. The results of this study are fascinating for several reasons. First, there are no pharmacokinetic studies demonstrating nearly similar bioavailability between T4 and T3. Second, there is no clear evidence to support the use of T3 for these patients. Finally, the use of oral T4 raises questions about the safety and efficacy of this approach.

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and T₃ (active hormone). The finding of increased T₃ and T₄ levels at all time points, even as early as 24 hours after surgery in the treatment group, is therefore distinctive. Second, most study subjects were infants younger than 4 months of age, and the dosing guidelines would recommend 6 to 8 μg/kg of T₄ for this age group; however, beneficial effects were seen at a lower dose in this study. Third, there were significant interleukin 6 and tumor necrosis factor α elevation in the placebo group relative to the treatment group, indicating a potential anti-inflammatory effect of T₄.

Some caution should be exerted in the interpretation and implementation of the results of Talwar and colleagues, because some limitations to this study were identified. It would have been beneficial to report objectively the nutritional status of subjects in this study, because it is essential for thyroid hormone hemostasis. Because of the intrinsic inotropic effect of thyroid hormone, the vasoactive inotropic score may not be a precise outcome measure in subjects receiving thyroid hormones. The measurement of cardiac output with transcutaneous monitors in infants has not been extensively validated. CI differences of 0.5 L/min/m² thus may be clinically negligible under most given circumstances.

Another important cautionary note from the interpretation of these results must be highlighted. The current treatment of children with congenital heart disease provides outstanding postoperative care with short ventilation times, short length of stay, and low mortality in most clinical circumstances. The presence of some morbidities, such as euthyroid sick syndrome, still persists in certain patients, however, and provides an opportunity for individualized care. In this day and age, it has become increasingly evident that patient-specific characteristics must guide decision making for the initiation of therapies. As an example, corticosteroid use has become widespread for pediatric cardiac surgical patients without a firm grasp of individualized patient characteristics and incomplete outcome measurements. Consequently, we as a field must resist the temptation of universal administration of a particular therapy. This is particularly important because neurohormonal axis manipulation may present an unknown number of risks in this young, developing population. We must rather focus on careful preoperative and postoperative phenotyping to identify completely the optimal therapy for these patients.

References