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The sick euthyroid syndrome in paediatric cardiac surgery patients

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Introduction
During critical illness, a spectrum of thyroid abnormalities is seen, collectively termed the sick euthyroid syndrome (SES) and primarily manifest as a low tri-iodothyronine state. The greatest derangement of the pituitary-thyroid axis occurs in the most severely ill patients [1]. In particular, interest has focused on patients of all ages undergoing cardiac surgery, from neonates to adults. The syndrome is well documented in paediatric cardiac intensive care patients [1, 2, 3, 4, 5, 6]. However, it is unclear whether the SES is an adaptive phenomenon to reduce metabolic rate, an important contributor to the disease process or just an associated marker of illness severity. Tri-iodothyronine replacement has been suggested. We review thyroid hormone administration in the critically ill paediatric cardiac patient with particular reference to cardiac pathophysiology, mechanisms of action of thyroid hormones and the current evidence for replacement therapy.

Thyroid physiology and the role of de-iodination
Thyroxin (T4) and 3,5,3′-tri-iodothyronine (T3) are synthesised by iodination of the tyrosyl residues of thyroglobulin and released from storage under the influence of thyroid-stimulating hormone (TSH). T4 can be considered primarily as the prohormone of T3 and exists in concentrations 100 times that of T3. However, T3 is 5 times more potent than T4 with a 10 times greater affinity for cellular thyroid receptors [7].

De-iodination of T4 accounts for 80% of T3 production, which occurs mainly in the liver, but also in most major organs except the cardiac myocyte. T3 stimulates increased oxygen consumption and protein synthesis, and affects carbohydrate, lipid and vitamin metabolism. The activity of the de-iodination enzymes is therefore crucial in the production of intracellular T3 and critical for the maintenance of normal cellular activity. Impaired de-iodination plays an important role in the sick euthyroid syndrome [8, 9, 10]. Metabolically inert 3′,5′,3′-tri-iodothyronine (reverse T3 (rT3)) is also produced from T4 in equal proportions to T3 in health [11] (Fig. 1).
Critical illness and the sick euthyroid syndrome

In critical illness, many abnormalities along the pituitary-thyroid axis have been demonstrated. These include an attenuated thyrotropin-releasing hormone (TRH) response, decreased TSH release, decreased serum binding, low thyroid-binding globulin (TBG), decreased total T4 and T3 levels, decreased 5′-mono-iodinase activity and decreased tissue uptake of T4. T3 cell uptake and, more significantly, production from T4 are impaired. rT3 is often elevated, indicating preferential conversion to rT3 or decreased clearance [12] (Table 1). The feedback response to a low T3 is blunted [13].

The most important effect is a critical decrease in T3 concentrations at cellular level [13]. This is the result of decreased hepatic uptake of T4 and decreased 5′-mono-iodinase activity leading to decreased peripheral conversion of T4 to T3 [8, 9]. The progression of severity of the syndrome parallels that of the concurrent illness with T3 falling to very low levels and rT3 rising [1, 8, 9, 13, 14]. rT3 is not known to be metabolically active [11, 15] but may play a role in inhibiting T4 to T3 conversion, exacerbating the T3 deficiency [15].

Critical illness is characterised by complex pro- and anti-inflammatory responses [16]. In concert with this, there are well-recognised alterations in endocrine responses, in particular the pituitary-adrenal axis [17]. It is not clear which of these responses are maladaptive. In this context, the SES may be an adaptive or maladaptive physiological response [9, 18].

An interesting, as yet unexplored, hypothesis may be that the SES fits into the paradigm of critical illness and multi-organ dysfunction as a complex non-linear system; application of this model [19] might indicate that the SES is an example of emergent order giving stability in the face of extreme physiological perturbation. Alternatively, it may be a marker of the loss of organ interaction, akin to the loss of heart rate variability, also correlated with poor outcome [19].

Paediatric cardiac intensive care and the sick euthyroid syndrome

Children, from neonates to adolescents, undergoing cardiac surgery exhibit the SES [1, 2, 3, 4, 5, 6]. The full spectrum of paediatric cardiac surgical procedures from early neonatal repairs and single ventricle palliations to adolescent surgical procedures induces the SES. An initial free hormone surge is seen on cardiopulmonary bypass (CPB) followed by low total and free T3 and T4 levels, high rT3 and normal to low thyroglobulin levels. In children, TSH levels are more often depressed than in adults [20, 21]. The nadir occurs at 24–48 h with recovery by day 5 [1, 2, 4, 6]. TSH recovery often precedes restoration in T3 and T4 levels. Axis suppression can sometimes last for 7 days [6].

The sickest patients show the greatest biochemical abnormality, those with complications showing more