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The use of hormonal therapy in pediatric heart disease

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1. ABSTRACT

The endocrine system plays an intricate role in the regulation and modulation of cardiovascular function. Several hormones including thyroid, mineralocorticoid, glucocorticoid, arginine-vasopressin (AVP), and growth hormone (GH) have been investigated as adjunctive therapies in pediatric cardiac disease. Thyroid hormone supplementation appears to be safe in neonatal and pediatric post-operative cardiac patients, but the benefits have been modest and inconsistent. Glucocorticoids appear to decrease the inflammatory response associated with cardiopulmonary bypass in children, but have little effect on clinical outcomes. The role of AVP in pediatric shock remains limited due to inconsistent trial results and its potential side effect profile. Although mineralcorticoids are commonly used to treat neurocardiogenic syncope, little to no benefit has been demonstrated in controlled trials. GH normalizes altered cardiac function in children who are GH deficient, but its effectiveness in the treatment of heart failure has been variable. Overall, the use of these hormones in a variety of pediatric cardiac conditions generally appears to be safe, but their efficacy for relieving symptoms, improving cardiac function, and improving clinical outcomes remains unclear.

2. INTRODUCTION

Modulation of cardiac function is a complex process, dependent on inherent, myocyte specific electrical and structural properties, as well as the surrounding hormonal milieu. Within this hormonal milieu, thyroid, mineralcorticoid, glucocorticoid, AVP, and GH all have important effects on cardiovascular function, Signs and symptoms of primary cardiac disease can often mimic deficiencies in these hormones and excess can often lead to significant impairment in cardiac function. This article summarizes the normal regulation of hormone secretion, the effects of these hormones on the cardiovascular system, and reviews the evidence supporting their use in a variety of pediatric cardiac disorders.

3. THE EFFECTS OF TRI-IODOTHYRONINE IN THE PEDIATRIC POST-OPERATIVE CARDIAC PATIENTS

3.1. Introduction

Thyroid hormone is crucial to the growth, maturation, oxygen consumption, nerve function, and metabolism at all stages of human development. Of all organ systems that thyroid hormone affects, the heart is one

of the most thyroid hormone responsive tissues in the body (1, 2). States of thyroid hormone deficiency (hypothyroidism) or excess (hyperthyroidism) cause altered cardiovascular function and potentially significant morbidity and mortality. Following cardiac surgery, an altered physiologic state ensues that mimics biochemical hypothyroidism resulting in changes to thyroid hormone metabolism and cardiac hemodynamics. Thus, thyroid hormone supplementation has been proposed as a means to improve cardiovascular function following cardiac surgery. The efficacy of thyroid hormone replacement in adult post-operative cardiac literature has been well described and is almost uniformly positive. The data in pediatric cardiac patients is accumulating and also showing promise for being a safe and efficacious intervention.

3.2. Regulation of thyroid hormone secretion and the mechanism of action

Secretion of thyroid hormone is tightly regulated via a feedback loop between the hypothalamus, pituitary and the thyroid gland. Thyroid releasing hormone (TRH) is synthesized and secreted from the hypothalamus and transported through the pituitary portal vascular system where it modulates release of thyroid stimulating hormone (TSH) from thyrotropes of the anterior pituitary. Potent stimuli for TRH secretion include changes in environmental temperature and inadequate thyroid hormone levels, while it is inhibited by somatostatin, cortisol, and dopamine. TSH, when bound to its G-protein coupled receptor in the thyroid gland, causes activation of cAMP-adenylate cyclase, which drives iodine trapping and eventual synthesis of thyroid hormone. Iodine is transferred from the capillary lumen through the cell where it is iodinates tyrosine residues on thyroglobulin through the activity of thyroid peroxidase. Coupling of monoiodotyrosine and diiodotyrosine residues forms triodothyroine or T3 (DIT + MIT) and thyroxine or T4 (DIT + DIT). T4 is preferentially secreted from the thyroid gland and is peripherally converted to T3 through activity of 5'-monodeiodinase. Both T3 and T4 feedback in a negative fashion at the level of the hypothalamus and pituitary gland to regulate TSH secretion within a tight range.

Thyroid hormone has well described effects on the cardiovascular system (1-4). The cellular effects of thyroid hormone on the cardiovascular system are mediated via nuclear thyroid receptors on both myocytes and vascular smooth muscle. The thyroid receptor (TR) is a member of the retinoic acid receptor superfamily, and encoded by two genes, TRalpha and TRbeta (5, 6). TRalpha1 appears to be the receptor that preferentially transmits the actions of T3 on the myocardium. TRalpha2 is a splice variant that does not bind T3 and serves as a negative protein for thyroid receptor signaling. The cardiac myocyte transports T3 preferentially to T4 via specific energy dependent transport proteins within the cell membrane (7, 8). Once inside the cell, T3 binds to its nuclear thyroid hormone receptor with great affinity. With its ligand bound, the thyroid receptor complex binds to thyroid hormone response elements in the promoter region of target genes resulting in transcriptional activation of these genes. Through this cellular action, T3 regulates a number of myocyte specific genes including myosin heavy chain, sarcoplasmic reticulum calcium-activated ATPase, phospholamban, alpha and beta adrenergic receptors, adenyl cyclase, protein kinase C and many ion channels. These genes directly and indirectly regulate myocyte structure, function, and the sensitivity of the myocyte to sympathetic nervous system stimuli. T3 also appears to have important extranuclear action on sodium, potassium, and calcium ion channels within the cell membrane (1). In rats, direct effects of thyroid hormone include increasing sodium-potassium ATPase pump activity in cardiac cells (9). Thyroid hormone effects are also mediated through changes in responsiveness within the sympathetic nervous system by increasing numbers of beta adrenergic receptors and their affinity for catecholamines (10). The sum of these cellular and extranuclear effects is a decrease in systemic vascular resistance, which results in increased cardiac ionotropy and chronotropy, and an overall increase in cardiac output.

3.3. Changes to thyroid hormone metabolism following cardiac surgery

Periods of critical illness and stress can result in altered thyroid hormone metabolism known as sick euthyroidism or non-thyroidal illness (11). This state is highlighted by a downregulation of 5'monodeiodinase and generalized suppression of hypothalamic-pituitary activity. This results in decreased levels of T4, TSH, and when severe, T3, along with a marked increase in reverse T3 levels from baseline. Several examples of cardiac conditions that are associated with the sick euthyroid state have been well described including congestive heart failure, following myocardial infarction, and following cardiopulmonary bypass (CPB) surgery (1, 12). Each of these conditions is characterized by a low cardiac output state, which mimics the changes in cardiovascular function observed in severe hypothyroidism. Whether the sick euthyroid state contributes to morbidity in these conditions or is an adaptive response remains an ongoing source of debate but has prompted several trials of thyroid hormone supplementation in these clinical scenarios. In a rat model of myocardial infarction, administration of thyroid hormone therapy following initial insult resulted in a significant increase in the ejection fraction and altered regulation of some T3 responsive genes compared to controls (13). T3 supplementation in adults under these circumstances has been safe and generally has shown modest benefits with respect to heart function and outcomes (14-18), though some studies did not show the same benefits (19). Thyroid hormone also appears to show important cardiac specific benefits in subtle forms of primary thyroid disease. For example, adult patients with subclinical hypothyroidism show improvements in diastolic function when placed on T4 therapy (20, 21).

Infants experience a similar low cardiac output syndrome following cardiac surgery, which also mimics a severe hypothyroid state. Neonates and children undergoing CPB show a similar yet more dramatic pattern of thyroid function abnormalities including a reduction in T3 levels, reduction in TSH levels, and elevation in reverse

T3 levels (22-26). Infants undergoing CPB reach a nadir of T3 levels at approximately 48 hours after bypass and tend to recover at 7 days. Severity of illness and complexity of surgery both appear to be inversely correlated with degree of hypoiodothyronemia (25, 27, 28). The etiology of this pattern of thyroid abnormalities is likely multifactorial and may include downregulation of 5'-monodeiodinase activity, reduction of thyroid binding globulin, and blood dilution during CPB. The hypothalamic-pituitary axis may also be downregulated by the use of dopamine or glucocorticoids. Lastly, an increase in the millieu of proinflammatory cytokines, specifically interleukin-6 (IL-6), following CPB has been shown to correlate with the reduction in T3 levels following CPB (29).

3.4. Trials of thyroid hormone supplementation in post-operative cardiac patients

Trials of thyroid hormone supplementation in the pediatric population have been relatively few in number and have suffered from small numbers of patients, which has dampened conclusions to this point. One of the first reports of T3 supplementation in the pediatric population involved a small case series of six young children and infants with complex heart lesions (30). In these patients, a rapid improvement in cardiorespiratory status was observed after treatment with T3 infusion, including increased cardiac output, decreased systemic vascular resistance, decreased use of inotropic agents, and a conversion to normal sinus rhythm. Portmann *et al*. performed a prospective study of 14 infants undergoing ventricular septal defect or tetralogy of Fallot repair, randomizing to infusion of T3 prior to cardiopulomary bypass and again after release of aortic cross-clamp vs. placebo (31). Unlike the untreated group, in which free T3 levels decreased as early as 1 hour after bypass, the treated group maintained pre-bypass levels for 72 hours after bypass. T3 repletion was accompanied by an increase in heart rate over the same timeframe. The increase in heart rate resulted in an improved peak pressure-rate product, implying an increase in cardiac output though this was not directly measured.

In the largest trial to date, Bettendorf *et al.* performed a double blinded, placebo controlled trial of 40 pediatric patients undergoing cardiac surgery and randomized patients to daily bolus infusions of T3 or placebo (22). In the T3 treated group, a significant improvement was observed in the therapeutic intervention scoring system by the 4th postoperative day, indicating a more rapid recovery with less intervention compared to placebo. Though a modest benefit in left ventricular (LV) function was seen in the T3 group, this effect was stronger in children undergoing longer operations with greater CPB time. Importantly, patients treated with T3 had no significant side effects. More recently, one-week old infants undergoing bypass surgery for ventricular septal defect repair or a Norwood procedure for a single left ventricle were treated post-operatively with a continuous infusion of T3 or placebo for 72 hours. A modest benefit in the composite clinical score was demonstrated in the treated group due to a more rapid time to negative fluid balance (32).

Whether the transient period of hypothyroidism following CPB represents a physiologic adaptation to minimize metabolic demands or a pathologic process that contributes to post-operative morbidity remains the subject of debate (33). Although initial studies of T3 supplementation have shown promise in improving cardiovascular parameters in children, T3 supplementation in the post-operative period has not been universally adopted (34). Studies to date have been small with diverse patient populations with variable cardiac lesions and procedure that may have made it difficult to apply findings universally. A large-scale (200 patients) study (The triiodothyronine for infants and children undergoing CPB [TRICC] study) is underway to further address this issue and the overall safety and efficacy of triiodothyronine supplementation in this population (35).

4. FLUDROCORTISONE TREATMENT FOR SYNCOPE

4.1. Introduction

Syncope is defined as a syndrome consisting of a relatively short period of temporary and self-limited loss of consciousness and postural tone caused by a transient diminution of blood flow to the brain. It is usually preceded by a very short period of premonitory symptoms and signs often referred to as presyncope (36, 37). By definition, there is usually rapid and complete recovery without the need for intervention to stop the episode. It has been estimated that 12-15% of children experience at least one syncopal episode prior to the end of adolescence (38, 39) and 25% during adolescence (40). Another study found that 47% of college students reported syncopal episodes (41). Most individuals experience only one syncopal episode, and it is estimated that 20-30% of the population will pass out some time in their lifetime.

Syncope may be categorized by etiology as cardiogenic, neurogenic, cerebrovascular, orthostatic, metabolic, vagal, or psychiatric (42-44). When these specific etiologies have been excluded, syncope may then be classified as neurally mediated, also referred to as neurocardiogenic, autonomic, or vasovagal syncope (42, 44-46). All of these terms are used to indicate a benign form of syncope and are occasionally referred to in a category of unexplained syncope, or syncope of unknown origin (42, 44-46). The etiology of syncope varies with age. In children and adolescents the etiology is largely neurocardiogenic with only a relatively small percentage of patients having a serious underlying condition (39, 40, 47, 48). In adults, the likelihood of a serious underlying condition causing syncope increases with advancing age and is greatest in those over 65 years of age. The recurrence rate of syncope is quite variable with 40-85% of individuals who seek evaluation having no recurrence. Furthermore, there is no clear relationship between the underlying cause of syncope and the recurrence rate. In the more serious categories, recurrences may be rare, while in the more

benign forms recurrences may occur frequently (49). When syncope is recurrent, treatment needs to be considered to prevent further recurrences, since even in the case of a benign etiology, the recurrences are distressing to the patients, affect their quality of life and can lead to injury or death if the loss of consciousness occurs during a potentially hazardous activity (50-52). Fludrocortisone is commonly recommended as a first consideration for pharmacological treatment of recurrent neurally mediated syncope in both children and adults.

4.2. The mechanism of action of fludrocortisone

Fludrocortisone (9-alphafluorohydrocortisone) is a synthetic corticosteroid with a potent mineralocorticoid and weak glucocorticoid activity at usual doses. It binds to the cytoplasmic mineralocorticoid receptor expressed in the epithelial cells of the distal nephron and other tissues (53). Ligand-bound mineralocorticoid receptor translocates to the nucleus and acts as a transcription factor, resulting in the activation of membrane transporters, such as the sodium potassium-ATPase pump and the epithelial sodium channel (54, 55). Its mechanism of action is to promote increased reabsorption of sodium and excretion of potassium and hydrogen ion from the distal tubules and collecting ducts of the kidney. The reabsorption of sodium facilitates osmotic movement of water into the vascular space (53).

4.3. Treatment for syncope

When a specific cause of syncope is identified, treatment is directed toward that underlying cause. However, the majority of cases of recurrent syncopal episodes in children and adults are attributed to a benign cause, most frequently neurocardiogenic. Although the exact mechanism underlying neurocardiogenic syncope is not fully understood, it is believed that the diminished cerebral blood flow is secondary to peripheral vascular pooling of blood, resulting in a decrease in systemic venous return and triggering a complex hemodynamic response culminating in hypotension, bradycardia, and loss of consciousness (45, 49). Once a diagnosis of recurrent neurocardiogenic syncope has been made, treatment aimed at prevention of recurrence is first focused on patient self-management through behavior modification. This includes avoidance of triggering events, recognition of premonitory symptoms, physical maneuvers to prevent blood from pooling in the extremities and maintenance of adequate hydration. Patients are also instructed to avoid caffeinated drinks and to increase their daily salt intake (42, 45, 46, 56). When recurrent syncope is unresponsive to behavioral modification strategies, pharmacologic treatment may be recommended. Multiple drug therapies have been employed with variable success, including the use of mineralocorticoid, beta-blockers, selective serotonin reuptake inhibitors, and alpha agonists (45, 46, 49, 56-58). The use of drug therapy for these patients is palliative and does not cure the tendency for recurrent syncope. There are no long-term, randomized, placebo-controlled trials of prophylactic pharmacologic intervention in the pediatric population or in adults. Most studies are short-term or are not randomized or placebo-controlled. Indeed, many patients seem to improve irrespective of which therapy is chosen (59, 60).

The use of mineralocorticoid therapy is generally the first choice for pediatric patients and among the first considerations in adults with recurrent neurocardiogenic syncope (40, 45, 46, 61, 62). Its use in neurocardiogenic syncope is predicated on the principle of increasing central blood volume through the increase in sodium and fluid retention and is supported by results of tilt-table testing (62-64). Other possible effects are increased vascular sensitivity to norepinephrine and an increase in the fluid content of vessel walls that increases their resistance to stretching (36, 40). Treatment with fludrocortisone is generally only used in conjunction with added salt. Side effects of fludrocortisone are generally both mild and uncommon and include fluid retention, weight gain, edema, and complaints of fatigue, nausea, insomnia, and chest pain (46, 61, 65). At more typical doses below 0.4 mg per day, electrolyte abnormalities are minimal (63). At higher doses, above 0.4 mg per day, more significant side effects may be seen, including hypertension, depression, headache, and hypokalemia (45).

While fludrocortisone is frequently suggested as an option for the pharmacological treatment of neurocardiogenic syncope, there is little in the way of evidence-based data to support its use. Most studies supporting the efficacy of fludrocortisone treatment are of short duration, are not blinded or placebo-controlled, and have relatively small sample size (60, 61, 63, 64, 66, 67). The only randomized, double-blinded, placebo-controlled trial of salt plus fludrocortisone demonstrated no difference between the placebo and the fludrocortisone groups in the rate of recurrence of symptoms (68). A large, prospective, randomized, placebo-controlled clinical trial of fludrocortisone for the prevention of neurally mediated syncope in older adolescents and adults is currently in progress (69). All studies need to be considered in light of the fact that the natural history of neurally mediated syncope is for spontaneous resolution, particularly in younger patients. Kapoor has concluded there is no clearly effective drug therapy for neurally mediated syncope (70). Therefore until new and convincing data becomes available, the continued use of fludrocortisone to treat neurally mediated syncope should be questioned and is likely to be used mainly for its safety and low cost, rather than for proven efficacy (42, 64, 65).

5. CORTICOSTEROIDS AFTER CARDIOPULMONARY BYPASS

5.1. Introduction

CPB is commonly accepted as a potent stressor for neonates. Anand *et al.* (1990) demonstrated significant elevations of plasma levels of epinephrine, norepinephrine, cortisol, glucagon, and beta-endorphin in infants following CPB (71). In addition, CPB has been shown to induce a systemic inflammatory response. Specifically, changes in complement activity, cytokine production, and neutrophil sequestration in the lungs have all been identified (72-76). This response is thought to lead to bleeding complications, thromboembolism, fluid retention, and organ dysfunction though the exact mechanism has not been delineated. The

last two decades have seen the use of corticosteroids following CPB to help modulate these effects.

5.2. The mechanism of anti-inflammatory action of corticosteroids

Hydrocortisone, methylprednisolone and dexamethasone are frequently used glucocorticoids without mineralocorticoid effects. Glucocorticoids bind to the cytoplasmic glucocorticoid receptor in target cells. Ligand-bound glucocorticoid receptor translocates to the nucleus and binds to the glucocorticoid-response elements of glucocorticoid-sensitive genes, regulating their transcription either directly or indirectly through interaction with other proteins (77, 78). Corticosteroids are known to have a variety of effects, including anti-inflammatory, immunosuppressive, and anti-proliferative properties. The anti-inflammatory activity of corticosteroids is due to their effects on the mediators of inflammation, e.g. leukotrienes, prostaglandins, kinins, and histamine (79). The decreased production, release, and activity of these molecules modulate the initial phase of inflammation. Following this corticosteroids inhibit margination and cell migration to areas of injury, as well as cause local vasoconstriction and decreased vessel permeability. The latter effects help to minimize capillary leak and swelling associated with inflammation.

5.3. Peri-operative steroid administration

The results of studies using steroids, including methylprednisolone and dexamethasone, in the peri-operative period have been mixed and controversial. The initial studies were done in adult patients. Dernek *et al.* administered intravenous methylprednisolone 30 mg/kg to adult patients undergoing valve replacement prior to the initiation of CPB (80). In comparison to the placebo control, patients who received methylprednisolone had lesser complement activation and pulmonary neutrophil sequestration. Other studies have also demonstrated decreases in post-CPB levels of tumor necrosis factor-alpha, IL-6, and IL-8 and increases in anti-inflammatory cytokines IL-10 and IL-1RA (81, 82).

More recent studies done in children failed to demonstrate a decrease in inflammatory markers in response to steroids. Gessler *et al.* prospectively studied infants undergoing CPB and compared those who had received prednisolone 30 mg/kg in the CPB priming solution with those who had not received steroids (83). This study was neither blinded nor randomized. There were no significant differences in the levels of IL-8 between the two groups. Nor were there any difference in clinical outcomes. Varan *et al.* prospectively randomized infants to receive either high dose (30 mg/kg) or low dose (2 mg/kg) methylprednisolone before the initiation of CPB (84). Both groups showed significant increases in their plasma levels of IL-6 and IL-8 following CPB with no statistically significant differences between the two groups. Similar to the previous study, there were no differences in clinical outcomes, such as duration of mechanical ventilation or length of stay in the pediatric intensive care unit, between the groups. Studies using dexamethasone also demonstrated mixed results with decreases in some inflammatory markers such as C-reactive protein, but no change in clinical outcomes (85).

A criticism of administration of methylprednisolone at the initiation of CPB has been that this may not allow sufficient time for the onset of action of steroids. To address this there has been some investigation into administration of steroids prior to surgery. Initial studies show more promise with this approach. Schroeder *et al.* compared the effects of preoperative and intraoperative methylprednisolone with the effects of intraoperative methylprednisolone alone in 29 children (86). The group that received pre- and intra-operative methylprednisolone had lower levels of pro-inflammatory cytokines, i.e. IL-6, and increased levels of anti-inflammatory cytokines, i.e. IL-10 though these effects decreased after 24 hours. In addition, children treated with pre- and intra-operative methylprednisolone had reduced fluid requirements, lower body temperature, and improved cardiac function as demonstrated by a smaller difference between arterial and venous oxygen saturation levels. In summary, although the use of steroids in infants and children in the peri-operative period is a relatively common practice, the literature remains controversial. This is a difficult area of study given the broad-spectrum of anatomic cardiac defects that exist and the varied age at which children must undergo reparative or palliative procedures.

5.4. Post-operative steroid administration

It has been suggested that the maximal inflammatory response in adults may not be seen until eight hours after CPB (87). In neonates and infants there is additional concern that a decrease in cardiac function also occurs hours after CPB (88). This had led to the inconsistent practice of steroid administration after surgery and CPB have been completed. To assess the validity of this practice and to examine evidence for presumed adrenal insufficiency, Ando *et al.* prospectively enrolled twenty infants less than 28 days old, who were scheduled for complete biventricular repair (89). Patients were randomized to either receive a seven-day tapering regimen of hydrocortisone that was initiated at the discontinuation of CPB or to receive a 5% glucose solution as placebo. The placebo group had inadequate serum cortisol levels (less than five micrograms/dL) in the first 72 hours, which gradually increased to 10.4 $\pm$ 3.8 micrograms/dL by day seven. Conversely, the treatment group maintained normal cortisol levels of 43.6 $\pm$ 8.4 micrograms/dL at 12 hours, which gradually decreased to 23.3 $\pm$ 7.2 microgras/dL by 72 hours. Though the normal cortisol response has not been clearly defined in neonates, common practice predicts levels of approximately 20 micrograms/dL when a neonate is under stress, such as following cardiac surgery. In addition to the differences in serum cortisol levels, there were significant clinical differences between the two groups, which they hypothesized were related to the cortisol levels. Specifically, patients in the treatment group had improved cardiac function, urine output, and net fluid balance. Thus, the study suggested a transient state of adrenal insufficiency after open heart surgery in neonates. However, there were no differences in the inflammatory

markers of IL-6 and C-reactive protein. Further studies are needed to define the post-operative stress response of neonates who have undergone cardiac surgery, and the safety of more prolonged post-operative use of steroids given the potential complications of immunosuppression and neurologic impairment seen in premature infants.

6. ARGININE-VASOPRESSIN IN SHOCK

6.1. Introduction

Severe septic and cardiogenic shock is associated with a high mortality. One of the invariable hallmarks of shock is overall tissue hyperpermeability secondary to microcirculatory/capillary leakage. A decrease in oncotic pressure is initiated by dilution of circulatory volume, protein breakdown (hypercatabolism) and extravascular leakage. Arginine-vasopressin (AVP) is a key hormone in the human body and is a potent vasoconstrictor, which has been used in vasodilatory shock when therapy with catecholamines and fluids has failed.

6.2. Regulation of arginine-vasopressin secretion and the mechanism of action

AVP, also referred to as antidiuretic hormone, is produced in the hypothalamus as a nanopeptide prohormone. It is secreted from the paraventricular and supraoptic nuclei in response to hemodynamic and osmotic stimuli, exerting vasoconstrictive, hemostatic and antidiuretic effects (90, 91). With severe hypovolemia, AVP activates V1 receptors in the vasculature to cause arterial vasoconstriction (92). Through V2 receptors in the renal tubules, it enhances free water retention when plasma osmolality increases. V2 receptors activate the cyclic adenosine monophosphate and protein kinase signal transduction cascade, causing increased permeability of renal collecting ducts, water retention and a higher urine osmolality. AVP also concentrates urine by altering the medullary concentration gradient through a separate urea transporter (93). In addition, it mediates the action of multiple hormones that affect water balance and blood pressure, including adrenocorticotropic hormone, prolactin, endothelin I, atrial natriuretic factor and angiotensin II (94-98). Some authors propose that AVP may also improve the sensitivity of adrenergic receptors in the vasculature (99). The ability of AVP to constrict the vasculature and retain free water forms the basis for its use as an adjunct to traditional pressors and inotropes in shock states. This article serves to summarize previous literature on the use of vasopressin in pediatric patients with shock. A description of the hormones mediated by AVP and their effects is beyond the scope of this review.

6.3. Therapeutic use of arginine-vasopressin in shock

Contrary to studies of patients in severe shock, AVP does not greatly affect regulation of arterial blood pressure under normovolemic states. Plasma AVP concentrations of 486 pg/ml (compared to physiological concentrations of 0.54-5.4 pg/ml) must be reached in order to demonstrate an increase in arterial blood pressure by 5-7 mmHg (100). AVP levels have been measured in vasodilatory shock, including septic shock and systemic inflammatory response syndrome post-cardiopulmonary bypass. It has been found in most studies that these patients have inappropriately low levels considering their degree of hypotension, though Lodha *et al.* showed the opposite in children with septic shock (101-106). These conflicting findings may be rationalized by reports that severe vasodilation causes a biphasic reaction in AVP levels with an initial rapid response where AVP spikes >500 pg/ml then decreases to inadequate values (107, 108). Multiple authors have demonstrated that depleted plasma AVP levels can be replaced with infusion of exogenous AVP, increasing values from 3.1 to 289.3 pg/ml (103, 109, 110). This would elevate plasma concentration in those with relative AVP insufficiency (105, 111). However, the correlation of AVP levels with blood pressure is a matter of controversy. Studies have shown that advanced vasodilatory shock can be reversed with exogenous AVP independent of pre-infusion plasma AVP concentrations (112, 113). Dunser *et al.* examined the relationship between plasma AVP levels with exogenous administration of AVP and its subsequent hemodynamic effects by comparing a combined vasopressin/norepinephrine infusion to a norepinephrine only control group in adults (113). No significant correlation was detected between plasma AVP concentrations, mean arterial pressure, or norepinephrine requirements.

Despite the evidence against any correlation of AVP levels with increased blood pressure, AVP has been widely used in the adult population as an adjunct to volume replacement, catecholamine and inotropic support for those in shock. Several authors note that exogenous AVP results in increased arterial blood pressure, successful weaning of vasopressor and inotropic support, along with improved urine output and decreased lactate levels (109, 114-121). In the pediatric population, AVP and its analogue terlipressin (TP) have been used in trials in septic shock, shock after cardiopulmonary bypass, cardiogenic shock, and trauma (101, 102, 112, 117, 120). TP is a synthetic analogue of AVP, distinguished by a longer half-life of 6 hours compared with 6 minutes for AVP. It is given in intermittent bolus doses, whereas AVP is often administered as a continuous infusion when used as an adjunct to pressor and inotropic support (122-126). Both TP and AVP have been used as rescue therapy for refractory shock (101). With a longer half-life, TP has been found to be more challenging in titrating appropriate levels for patients with hemodynamic instability (127). Transient improvement in blood pressure, however insufficient to prevent death, was seen in neonates given AVP for refractory hypotension after cardiac surgery and with cardiogenic shock, suggesting that AVP is unlikely to benefit shock associated with ventricular dysfunction (120). Studies of neonates with catecholamine-refractory vasodilatory shock after CPB who were administered rescue therapy have shown promise – a significant increase in blood pressure was noted from 49±8 to 69±7 mmHg (128). Other authors noted a similar increase in blood pressure within 15 to 60 minutes of administration (109, 117, 120-126, 128-134). Lechner *et al.* showed a significant increase in urine output in neonates post-CPB from 1.33±0.82 to 2.17±0.09 cc/kg/h, which is supported by several authors (109, 117, 128, 131-133). Rosenzweig *et*

al. and Efrati *et al.* did not demonstrate a similar effect (120, 130). Many studies describe a decrease in the volume of crystalloids and the dose of vasopressors required within hours of starting AVP or TP (117, 121-126, 128-130, 132-134). There is also a decrease in serum lactate values and an increase in mixed venous and arterial oxygen saturations in patients who survive vasodilatory shock after exogenous AVP administration (122, 128, 129, 132, 133). However, a systematic review by Meyer *et al.* (of multiple case series, case reports, retrospective analysis, and few prospective trials) concluded that there is no strong evidence to support the use of AVP or TP in children with refractory shock, based on the levels of evidence outlined by the Oxford Centre for Evidence-based Medicine (101).

Despite improvements in arterial blood pressure with AVP infusion, the mortality rates are still high as expected in the critically ill. A review by Meyer *et al.* shows a pooled overall mortality of 52/109 in a heterogenous study population of pediatric patients with septic, cardiogenic and cardiocirculatory shock, treated with either AVP or TP (101). The survival rate is especially poor in individuals with poor cardiac contractility and ventricular dysfunction (120, 130, 133). This high mortality rate is reflective of critical illness, where patients suffer end-organ failure and are near death, where AVP is given as a last resort rescue therapy. There is a possibility of improvement in the effectiveness of AVP if introduced earlier in the course of vasodilatory shock (128, 130). This conjecture is supported by a large study of adults in septic shock that suggested a positive effect when AVP infusion began prior to increasing doses of norepinephrine beyond 0.6 micrograms/kg/min (118).

There are few studies describing recommended doses of AVP in children and neonates. In adults, a dose range between 0.004 to 0.1 U/kg/min is adequate for hemodynamic support, where the side effect profile is not worsened. With limited pediatric reviews, doses have been extrapolated from adult ranges as 0.00006 to 0.001 U/kg/min, titrated to achieve the target systolic blood pressure for age (128). Multiple studies have not detected any adverse effects secondary to infusion of AVP in the pediatric population (109, 117, 122-124, 128, 131, 133, 135, 136). However, other literature reveals that it may cause severe pulmonary, splanchnic and peripheral vasoconstriction, as well as potential neurological deficits. Although some reports describe endothelium dependent pulmonary vasculature dilation with AVP, others note pulmonary vasoconstriction where right ventricular function is worsened (137-139). The effect of AVP on the splanchnic vasculature remains controversial (140). Neonates receiving AVP post-cardiopulmonary bypass did not suffer from necrotizing enterocolitis, mesenteric ischemia or intolerance to enteral nutrition (128). However, van Haren *et al.* describe AVP induced gastrointestinal hypoperfusion in norepinephrine-dependent adults with septic shock, while others report cases of hepatic necrosis possibly caused by AVP (133, 141). A spectrum of adverse effects on the extremities have been noted, from peripheral vasoconstriction to cutaneous ischemia and deep tissue necrosis. Lechner *et al.* demonstrated no such events in their study of neonates in catecholamine resistant vasodilatory shock, though their study was limited to patients post-CPB (128). Liedel *et al.* examined cases of peripheral vasoconstriction in children that did not progress to skin necrosis where the dose of AVP exceeded 0.007 U/kg/min (117). Reports of severe cutaneous ischemia are documented, along with necrosis of the extremities requiring amputation, most notably in patients with severe meningococcal disease or who had received instrumentation of their femoral arteries (126, 129, 134). One study has shown neurological deficits after administration of AVP, including partial anopsy and dysmetria (134). It is unknown whether these findings were associated with cerebral or cerebellar vasoconstriction. The possible mechanism that may be involved in vasoconstriction includes direct activation of V1 receptors located on smooth muscle cells. However, this effect is compounded by vasodilatory responses in the major cerebral arteries secondary to nitric oxide release by AVP. Until there is more data to suggest that AVP does not cause severe vasoconstriction-induced events in pediatric patients, it may be worthwhile to continue trials at lower doses or to defer its use altogether in higher risk circumstances. This would include patients with failing ventricular function and pulmonary hypertension, known splanchnic perfusion deficits (including neonates with a patent ductus arteriosus causing diastolic runoff into the pulmonary artery), as well as peripheral vascular compromise (including meningococcal disease and previous femoral artery catheterization) (117, 126, 128, 129, 133, 134, 137-141).

7. THE EFFECT OF GROWTH HORMONE ON CARDIAC FUNCTION

7.1. Introduction

Treatment with recombinant human growth hormone (GH) has beneficial effects not only on linear growth in children, but also bone mineral density and metabolic parameters, such as body composition and lipid profile during and beyond childhood (142, 143). That the heart may be the target of GH action has been suggested by animal studies and supported by epidemiological data that have shown that adults with hypopituitarism are at increased risk of cardiovascular death (144-146). Since these patients frequently have multiple hormonal deficiencies, it is difficult to discern the contribution of individual hormones. Given that GH is frequently deficient in these patients, it seems plausible that it could contribute to this cardiovascular risk. Several clinical studies that have been performed to address this issue provided conflicting results. This review focuses on the effect of GH treatment specifically on cardiac structure and function in children and young adults. Discussion of other cardiovascular risk factors is beyond the scope of this paper.

7.2. Regulation of growth hormone secretion and the mechanism of action

Human GH is a 191-amino acid single chain protein. The majority of pituitary GH exists in a 22-kd form, although smaller variants, produced by alternative

splicing, have also been identified (147, 148). GH is secreted in a pulsatile fashion by the somatotropes of the anterior pituitary. Neuroregulation of GH secretion is complex and involves a number of neuropeptides, neurotransmitters, metabolic substrates, other hormones, as well as cholinergic and adrenergic input (149). The main hypothalamic regulatory peptides are GH-releasing hormone (GHRH) and somatostatin (somatotropin release-inhibiting factor, SRIF). Other regulators of GH secretion are synthetic GH-releasing peptides (GHRPs), for example hexarelin (149, 150) and Ghrelin, a peptide produced predominantly by the stomach (151), both having potential therapeutic implications (152-155).

Binding of GH to its membrane-associated receptor induces receptor dimerization and activation of JAK2 (Janus kinase 2) tyrosine kinase (156). This is followed by activation of STATs (signal transducers and activators of transcription) and recruitment of other signaling pathways (157). The main, although not sole, mediator of growth-promoting action of GH is insulin-like growth factor 1 (IGF-I), which is synthesized in the liver as well as other tissues where it may act in autocrine/paracrine fashion. The majority of IGF-I that circulates in the serum is bound to the IGF binding protein-3 (IGFBP-3) and acid-labile subunit (ALS), which prolong the half-life of IGF-I and regulate its delivery to tissues (158).

Both GH and IGF-I receptors are present in the heart (159-162). Studies in animal models have shown that GH and/or IGF-I can induce LV hypertrophy and improve cardiac function in normal rats (163) as well as in experimental heart failure (164-166). The increase in myocardial mass in response to GH/IGF-I is due to myocyte hypertrophy and not an increase in interstitial tissue as demonstrated by histological analysis of cardiac tissue in rats (163, 164). This has also been reported in humans when a myocardial biopsy was obtained in a patient with dilated cardiomyopathy after treatment with GH (167). Improvement in LV function was accompanied by a dramatic recovery of myofibrillar content in myocardiocytes. Myocyte hypertrophy in response to GH is accompanied by a significant induction of IGF-I expression in cardiac myocytes, suggesting that IGF-I may act in autocrine/paracrine fashion in the heart (168, 169). Myocyte hypertrophy in response to IGF-I is mediated through induction of expression of muscle-specific genes (170). IGF-I enhances myocardial contractility by sensitizing the myofilament to Ca^{2+} without increasing intracellular Ca^{2+} availability as shown in rat whole hearts and ferret papillary muscles (171). This positive inotropic effect is blocked by concomitant administration of IGFBP-3. Administration of GH also increases contractility and intracellular calcium transients in myocytes from rats with chronic postinfarction heart failure (172). In addition, IGF-I has a cardioprotective effect by inhibiting cardiomyocyte apoptosis after myocardial ischemia and reperfusion in mice (173)

7.3. GH treatment of cardiac dysfunction in GH deficiency

A number of studies in adult patients have shown that GH deficiency (GHD) may result in reduced LV mass, LV systolic function, and exercise capacity (174-177). Some patients with GHD, particularly those with adult-onset GHD, may have a normal LV mass and systolic function, but abnormal LV diastolic function and ischemic-like ST segment changes during exercise testing (178, 179). The observation of impaired cardiac function in adults with GHD raised a question whether children and adolescents may exhibit some of the early manifestations of presumed adverse effects of GHD on the heart. This question becomes particularly relevant when a decision has to be made about discontinuation of GH treatment in adolescents who have completed linear growth versus transition to adult dosing. Colao *et al.* found that as early as 6 months after withdrawal of GH replacement, there was a decrease in LV mass index and diastolic filling in GH deficient adolescents (180). There was also a slight decrease in LV ejection fraction that approached statistical significance. The latter parameter was significantly lower in patients with multiple pituitary hormone deficiencies compared to patients with isolated GHD. Thus, this study demonstrated that discontinuation of GH treatment in adolescents reduces cardiac size and diastolic filling. Reduction in LV mass can be detected at even younger ages as shown in studies of GH deficient prepubertal children, although typically without obvious functional consequences at this age (181-183). It should be noted, however, that impairment of cardiac structure and/or function in pediatric patients with GHD is neither profound nor uniform and that no differences between GH deficient subjects and controls have also been reported (184).

The clinical studies in adults with GHD revealed variable effects of GH treatment on cardiac output, ejection fraction, and exercise duration with positive effects being reported by some (175, 177, 185), but none or heterogenous effects on various parameters of cardiac function by others (186-189). To reconcile some of this data, Maison *et al.* conducted a meta-analysis that included a total of 468 patients over 17 years of age with documented GHD who participated in 16 trials conducted between 1991 and 2002 (190). These included 9 randomized, blinded, placebo-controlled trials and 7 open label studies with echocardiographic assessment of cardiac function. A significant increase was found in LV mass, interventricular septum thickness, LV posterior wall, end-diastolic diameters, and stroke volume in GH-treated patients even though GH dose (0.1-0.45 U/kg per week), duration of treatment (only 3 studies with a duration of treatment over 1 year), and study populations (age of onset of GHD, degree of cardiac dysfunction at baseline) varied among the studies.

Colao *et al.* prospectively studied cardiac mass and performance in 10 adolescents with GHD immediately prior to GH discontinuation, 6 months off therapy, and 6 months after treatment was restarted (180). At study entry, GH deficient adolescents had normal indices of cardiac size and function. Six months after discontinuation of treatment, there was a decrease in LV mass index and diastolic filling in the GHD group compared with controls, although both parameters remained within the normal range. Both parameters returned to baseline following GH reinstitution. Only a few studies have investigated the effect of GH

treatment on cardiac structure and function in prepubertal children. Shulman *et al.* conducted a prospective, uncontrolled study of 10 children with classical GHD who received GH treatment for 1 year (181). LV mass index was reduced at baseline in 5 children and increased into the normal range with GH therapy. Similar findings were reported by Salerno *et al.* in a case-control study that involved 12 GHD children who were treated with GH for 1 year (182). At study entry, GHD children had a significant decrease in cardiac size, which normalized on GH treatment. Cardiac function was not changed at baseline or during treatment. In a more recent prospective, open, case-control study Salerno *et al.* investigated the effects of a 2-year trial of GH treatment on cardiac mass and function in 30 children with GHD (183). At study entry, children with GHD had reduced LV mass index, but normal systolic and diastolic function. LV mass index increased after 1 yr of GH replacement and remained similar to that of controls at year 2. The increase in LV mass correlated with the increase in IGF-I levels. Cardiac function did not change during treatment. Thus, these studies have shown that the reduction in cardiac size in GH deficient pediatric patients normalizes in response to GH treatment. Cardiovascular parameters were assessed by echocardiography in these studies.

7.4. GH treatment of heart failure due to dilated cardiomyopathy

The effectiveness of GH in adults with heart failure due to dilated cardiomyopathy (DCM) has been variable. Several studies have shown significant improvement in cardiac morphology and function, manifesting as an increase in LV mass and ejection fraction, reduction in end-systolic wall stress, and improvement in exercise capacity and cardiopulmonary performance (167, 191-193). Perrot *et al.* reported that both the changes in LV mass and ejection fraction correlated with increases in IGF-I, such that the changes in the ejection fraction could be predicted by the increases in IGF-I levels (193). A study by Osterziel *et al.*, however, did not demonstrate any functional improvement after three months of treatment with GH, even though there was a significant increase in LV mass in response to treatment (194). A potential benefit of a longer duration of GH treatment could not be excluded by this short-term study.

DCM is one of the most common causes of heart failure in children and the main indication for cardiac transplantation. Very few reports exist on the effectiveness of GH in DCM in children, mostly in the form of case reports, which either suggest a positive effect (195, 196) or no effect (197). The first prospective, randomized, partially blinded, crossover trial was conducted by McElhinney *et al.* (198). Eight patients with DCM (younger than 19 years) received GH treatment for 6 months along with conventional therapy or conventional therapy alone. Patients were then crossed over to the other treatment arm. The shortening fraction did not change significantly on treatment, although the increase in ejection fraction approached statistical significance. A change in LV mass was not significant. Only LV end-diastolic volume z score significantly increased during the treatment phase. Interestingly, IGF-I levels remained higher than at baseline not only during GH treatment, but also 6 months after its discontinuation. This was accompanied by a significant increase in the shortening fraction and a reduction in LV end-systolic stress after GH treatment was stopped, perhaps suggesting beneficial effect of prior GH exposure. One of the limitations of this study was its small size, which limited its statistical power, but it did show trends toward improved systolic function, an observation that requires further study.

One of the factors that may need to be considered in future studies is individualized GH dosing to optimize IGF-I levels, the importance of which has been demonstrated in adult patients with chronic heart failure due to coronary artery disease (199). A dose-dependent increase in IGF-I and IGFBP-3 levels in response to GH treatment correlated positively with LV ejection fraction in these patients. It is also noteworthy that heart failure itself may lead to alterations in GH/IGF-I axis, leading to decreased serum levels of IGF-I and IGFBP-3, either due to reduced GH secretion or resistance. A relative GH deficiency state is most likely due to alteration of neuroregulation of GH secretion due to activation of other neurohumoral processes in heart failure, such as activation of central sympathetic outflow, which activates neurons in the paraventricular nucleus of the hypothalamus, resulting in increased somatostatin release (199-203). The role for increased somatostatinergic tone is supported by the observation that patients with DCM have a reduced GH response to GHRH, but normal response to hexarelin (204), which may stimulate GH secretion independent of GHRH (149). In contrast to reduced GH secretion, some patients with heart failure, particularly those with cachexia, have GH resistance, which may limit their responsiveness to GH treatment (205) and account for the variable results obtained in published studies. Therefore, it would seem appropriate to determine the nature of GH/IGF-I axis disturbance and the responsiveness to GH prior to the use of GH.

8. SUMMARY AND PERSPECTIVE

It is clear that the hormones discussed in this review have important effects on cardiac muscle and peripheral vasculature. Despite these known physiologic effects, the therapeutic application of these hormones in pediatric cardiac disease has resulted in inconsistent outcomes. In many cases, this is in contrast to the available adult data. These inconsistencies may stem from the limited number of children studied and the lower occurrence of pediatric cardiac disease in comparison to similar adult cardiac disease. For example, the numbers of patients eligible for a trial of thyroid hormone in adults following myocardial function is vastly greater and more uniform than a similar trial targeting children with a congenital heart lesion requiring a complex surgical repair. Alternatively, the inconsistent results observed to this point may also highlight important differences between adults and children, in particular the neonates. Many of these hormones have different effects on the still developing cardiovascular system, and less benefit clinically than what

has been observed in the fully mature heart. Importantly, with the exception of perhaps AVP, the risk-benefit ratio is favorable for these hormones and various applications of their use in different pediatric populations and conditions should continue to prove they are both safe and efficacious.

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Abbreviations: ALS: acid-labile subunit; ATP: adenosine triphosphate; AVP: arginine-vasopressin; CPB: cardiopulmonary bypass; DCM: dilated cardiomyopathy; GH: growth hormone; GHD: growth hormone deficiency; GHRH: growth hormone-releasing hormone; GHRP: growth hormone-releasing peptide; IGF-I: insulin-like growth factor 1; IGFBP-3: IGF binding protein-3; IL: interleukin; JAK2: Janus kinase 2; LV: left ventricular; SRIF: somatotropin release-inhibiting factor; STAT: signal transducer and activator of transcription; T3: triodothyroine; T4: thyroxine; TP: terlipressin; TR: thyroid receptor; TRH: thyroid releasing hormone; TSH: thyroid stimulating hormone

Key Words: Thyroid Hormone, Fludrocortisone, Vasopressin, Growth Hormone, Heart Failure, Dilated Cardiomyopathy, Cardiac Surgery, Cardiopulmonary Bypass, Syncope, Shock

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