

Thyroid

HPT-AXIS AND THYROID HORMONE ACTION

Elevated Pre-Op Thyrotropin Levels Are Associated With Increased 30-Day Mortality in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass

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SAT-LB80

BACKGROUND: The association between thyroid dysfunction and postoperative mortality is contentious. Thyroid function is frequently depressed during and after cardiopulmonary bypass surgical procedures, and this may adversely affect myocardial performance and postop outcome. **OBJECTIVES:** To study i) the changes and clinical significance of serum thyroid hormones during cardiopulmonary bypass (CPB), and ii) the association between biochemically assessed peri-op thyroid function and 30-day mortality after CBP. **STUDY DESIGN:** Prospective Cohort Study. **SUBJECTS:** 279 patients undergoing various cardiac surgeries under cardiopulmonary bypass. **METHODS:** All consenting patients undergoing open heart surgery in last five years at a tertiary care centre in North-India were studied. The thyroid hormone levels (Total T3, T4 and TSH) were measured before admission, and postoperatively on Day 1 & 7, and 3 months following surgery. The patients' gender, age, weight, body mass index, heart disease details, previous cardiac surgeries, and cardiac surgery-related data such as pump time, aortic clamping time, hypothermia duration, postoperative hemodynamic status and postoperative use of inotropic drugs were recorded and analysed. Patients were classified as having biochemically overt or subclinical hyperthyroidism or hypothyroidism, normal thyroid function, or non-classifiable state based on preoperative thyroid-stimulating hormone and total T4 values. Outcome data were collected from hospital records. Biochemical thyroid dysfunction was not systematically treated. Outcomes measured were length of ICU stay, postoperative complications and 30-day mortality. **RESULTS:** There was significant changes in thyroid function in patients undergoing cardiopulmonary bypass surgery (Fig 1). All patients showed a decrease in T3, T4 and TSH after surgery. Post-op complications were observed in 137 patients (49%) most common being atrial fibrillation (34%) followed by acute kidney injury (23%), infections (18%), dyselectrolytemia (7%), bleeding (1.4%) and ARDS (1.4%). Of 263 patients followed, eventually 26 patients expired with a mortality rate of 8.89% (95% CI, 0.4 - 19.4). Perioperatively, there was a significant correlation between 30-day with type of surgery (r, 0.26), aortic clamp time (r, 0.45), CBP time (r, 0.48), number of inotropes used (r, 0.57), hours of mechanical ventilation (r, 0.4), ICU stay (r, 0.13) and post-op complications (r, 0.24), as well as with the reduction in the thyroid hormone levels; 17 (7%), 3 (20%) and 6 (46%) patients of those with pre-op TSH level of <6.5, >6.5 and >10.5 mIU/L expired (p <0.001). **CONCLUSION:** Pre-op thyroid dysfunction is associated with increased

mortality in patients undergoing cardiac surgery with CBP. Excess mortality with elevated serum TSH levels suggests the importance of timely detection and intervention in individuals with thyroid dysfunction undergoing cardiac surgery. Table of Contents

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oFigures in parenthesis indicate \pm Standard Deviation, unless indicated otherwise

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Reproductive Endocrinology

HYPERANDROGENISM

Androgenic Profiles of Patients With Severe Insulin Resistance

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Background Patients with severe insulin resistance have ovarian hyperthecosis, high testosterone (T) and minimal adipose tissue. Recent studies have found elevated levels of 11-oxygenated (11-oxy) androgens in women with polycystic ovary syndrome (PCOS) compared to age and sex-matched controls. 11-oxy-androgens are produced by CYP11B1, an enzyme expressed predominantly in the adrenal, with minor ovarian expression. We analyzed 11-oxy-androgens in women with severe insulin resistance. **Methods** We performed retrospective analysis of women with severe insulin resistance (lipodystrophy or insulin receptor defects) seen at the NIH and identified 19 patients with testosterone \geq 80 ng/dl (immunoassay) and available serum samples. Quantitation of androgens was performed by LC-MS/MS and compared to age, sex and BMI-matched controls. Data between groups was compared using non-parametric Mann-Whitney U test. Correlation analyses utilized the Pearson and Spearman's rho. **Results** Median patient age was 18yrs (IQR 17-26) with median fasting insulin of 63mcU/ mL (IQR 40-184). Serum insulin correlated strongly with fold elevation of T in patients relative to controls (r= 0.47, P=0.04). Median levels of all androgens except 11-hydroxytestosterone (11OHT) were significantly higher in patients than controls, including 11-ketotestosterone (11KT), a clinically relevant androgen in both congenital adrenal hyperplasia and PCOS [69 ng/dl (IQR 27-82) vs 24 ng/dl (IQR 16-40), P < 0.001]. 11KT/ T was lower in patients (0.30, IQR 0.12-1.15) compared to controls (1.1, IQR 0.41-1.5, P = 0.04).

All 11-oxy-androgens correlated with each other (r_s range: 0.6-0.8, $P < .05$) in both groups. There was no difference in the proportionate contribution of 11-oxy-androgens to the total circulating androgenic pool in patients vs. controls. **Conclusion:** Elevated 11-oxy-androgens in patients with severe insulin resistance suggests that both adrenal and ovarian androgens are upregulated by hyperinsulinemia. Lower 11KT/T in patients compared to controls despite higher 11-oxy-androgens than in controls is consistent with predominant ovarian T excess in patients with severe IR. Correlation between insulin and fold elevation of T relative to controls supports hyperinsulinemia as the cause of high T in states of hyperinsulinism. **Acknowledgement:** This research was supported by the Intramural Program of NIH Clinical Center and NIDDK.

Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS II

RAAS Triple-A Analysis for the Screening of Primary Aldosteronism

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Primary aldosteronism (PA) is recognized as the most frequent cause of secondary hypertension, and its screening is expected to become a routine evaluation in most patients with hypertension. The interference of antihypertensive therapies with the aldosterone-to-renin ratio (ARR) during screening process is a major confounder. Renin-Angiotensin-Aldosterone System Triple-A (RAAS Triple-A) testing is a novel mass-spectrometry based assay for quantification of Angiotensin I (Ang I), Angiotensin II (Ang II) and Aldosterone in a single sample of serum by RAAS equilibrium analysis. Obtained hormone levels are used to calculate markers for plasma-renin-activity (PRA-S, Ang I + Ang II), plasma angiotensin-converting-enzyme activity (ACE-S, Ang II-to-Ang I ratio) and adrenal function (AA2-Ratio, Aldosterone-to-Ang II ratio), with the latter being useful to screen for PA in hypertension. We performed a comparative evaluation of the diagnostic performance of the AA2-Ratio and 5 renin-based diagnostic ratios, differing in methods to determine aldosterone levels and renin activity in a cohort of 110 patients with hypertension (33 patients with confirmed primary aldosteronism and 77 with essential hypertension). All ratios showed comparable areas under the curves ranging between 0.924 and 0.970 without significant differences between each other. The evaluation of the ACE-S revealed persistent drug intake in some patients as cause for suppressed renin-based diagnostic ratios, while the AA2-Ratio remained unaffected. The Youden index optimal cutoff value for the AA2-Ratio was 6.6 ([pmol/L]/[pmol/L]) with a sensitivity of 90% and a specificity of 93%, proving non-inferiority compared with the ARR while pointing to the potential for an interference-free application in patients under ACE inhibitor therapy. This study shows for the first time the accuracy and reliability of

RAAS Triple-A analysis for the screening of primary aldosteronism that can be applied in clinical routine.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Insulin Sensing by Astrocytes Is Critical for Normal Thermogenesis and Body Temperature Regulation

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SAT-LB107

The important role of astrocytes in the central control of energy balance and glucose homeostasis has only recently been recognized. Changes in thermoregulation can lead to metabolic dysregulation, but the role of astrocytes in this process is not yet clear. Therefore, we generated mice congenitally lacking insulin receptors (IR) in astrocytes (IRKO^{GFAP} mice) to investigate the involvement of astrocyte insulin signaling. IRKO^{GFAP} mice displayed a significant decrease in energy expenditure and a striking decrease in basal and fasting body temperature. When exposed to cold, however, they were able to mount a thermogenic response. Brown adipose tissue in IRKO^{GFAP} mice exhibited increased adipocyte size, more apoptosis, loss of innervation, and decreased β AR3 expression levels. These findings identify a novel role for astrocyte insulin signaling in the development of normal body temperature control and sympathetic activation of BAT. Targeting insulin signaling in astrocytes has the potential to serve as a novel target for increasing energy expenditure.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

The Spectrum of Genomic and Transcriptomic Alterations in ACTH-Producing and ACTH-Silent Corticotroph Adenomas

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Corticotroph adenomas (CA) are rare pituitary tumors that impose several challenges in clinical management - CA are difficult to diagnose, often recur, and are associated with high morbidity and mortality. CA are characteristically Tpit-positive and PIT1-negative and comprise ACTH-producing (Cushing's disease (CD)) and ACTH-silent (AS)