Variable and Pulsatile Circulating Aldosterone Levels in Primary Aldosteronism: Implications for Diagnosis and Sub-Type Differentiation

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Introduction: Considerable intra-individual variability in circulating aldosterone levels has been observed in patients with primary aldosteronism (PA). The magnitude and implications of this phenomenon are not well characterized.
Objective: To evaluate the acute variability in aldosterone in patients with confirmed PA.
Methods: 373 patients with confirmed PA underwent adrenal venous sampling (AVS) after appropriate catheterization of bilateral adrenal veins. Peripheral venous aldosterone levels were measured 2 hours prior to AVS while in supine posture. After anesthesia induction with fentanyl and midazolam, AVS was performed while in the same supine posture, and aldosterone levels were drawn from the inferior vena cava (IVC) and in triplicate from the bilateral adrenal veins over 10 minutes. Differences between the pre-AVS and intra-AVS IVC aldosterone levels were analyzed, and regression models used to identify independent predictors of change. Coefficients of variation (COV) between triplicate aldosterone levels in each adrenal vein were calculated.
Results: 81% of patients demonstrated a decrease in aldosterone concentration from pre-AVS to the intra-AVS IVC measurement. The mean decrease in aldosterone was 10.5 ng/dL (95% CI: 7.6–13.3) and the mean relative decrease in aldosterone was 39% (95% CI: 27–51%, P<0.0001). The absolute decrease in aldosterone was striking, with 48% of patients who had a decrease in aldosterone exhibiting an IVC aldosterone of less than or equal to 5 ng/dL. The absolute decrease in aldosterone was significantly associated with a higher aldosterone level (p<0.001) and lower systolic blood pressure at diagnosis (p=0.02). A wide variation in triplicate aldosterone values was seen in the span of 10-minute sampling, ranging from 1–300%, with COV of 21.0% in the left adrenal vein and 25.0% in the right adrenal vein. If the lowest of three aldosterone-to-cortisol (A/C) ratios on the dominant side and highest of three A/C ratios on the contralateral side were used instead of the average of the three values, the interpretation of the AVS would have changed from unilateral PA to bilateral PA in 15.9% of cases.
Conclusions: These findings underscore the pulsatile and variable nature of circulating aldosterone levels in patients with *bona fide* PA. Aldosterone levels substantially declined in 81% of patients within a period of 2 hours while maintaining a fixed and supine posture. In half of these patients, aldosterone levels declined to 5 ng/dL or below, a threshold typically considered incompatible with PA. Further, adrenal venous aldosterone levels exhibited large variations on repeated sampling within a 10-minute span that could have influenced the interpretation of sub-type differentiation in nearly 16% of cases. Single circulating aldosterone values lack precision and reproducibility and may result in incorrect diagnosis and sub-type differentiation.

Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Polycystic Ovary Syndrome (PCOS) in Adolescent Girls:Toward a Simple On-Treatment Predictor of Post-Treatment Ovulation Rate

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There is no approved treatment for adolescent girls with PCOS. The vast majority of these patients are guided into a trajectory that starts with oral contraceptive (OC) treatment, leads into oligo-anovulatory subfertility, then into the use of assisted reproductive techniques, and ultimately into pregnancies with a double-to-triple risk for complications (such as gestational diabetes, preeclampsia and preterm birth) potentially with lifelong sequelae in the offspring.
Evidence is converging into the insight that adolescent PCOS is frequently driven by hepato-visceral fat excess ("central obesity") ensuing from a mismatch between (rather restrictive) prenatal and (rather abundant) postnatal nutrition, on a background of genetic susceptibility *(Trends Endocrinol Metab 2018;29:815)*. This insight has prompted the exploration of an alternative PCOS treatment that aims at reducing the central-fat excess (without causing weight loss in non-obese girls) in order to normalize the entire phenotype, including ovulation rate.
So far, this alternative approach has been tested in two randomized controlled pilot studies that were performed in non-obese girls with PCOS and with no need for contraception (total N=62; age 16 yr; BMI 24 Kg/m^2; treatment for 1 year; ovulation assessment during the post-treatment year). In these studies, the effects of an OC were compared to those of SPIOMET, which is a low-dose combination of spironolactone (= a mixed anti-androgen and -mineralocorticoid, also activating brown adipose tissue; *Diab Ob Metab 2019;21:509*), pioglitazone and metformin (= two insulin sensitizers acting through different mechanisms).
Pooled results of the pilot studies confirm the first report *(J Adolesc Health 2017;61:446)* that SPIOMET has more normalizing effects than OC; there were approximately 3-fold more ovulations post-SPIOMET than post-OC; normovulation occurred only post-SPIOMET; anovulation was >10-fold more frequent post-OC.
Pooled results also disclosed two new features of adolescent PCOS: low concentrations of circulating CXCL14 (= a brown adipokine, signaling activity in brown adipose tissue; *Cell Metab 2018;28:750*) and miR-451a (= an inhibitor of THRSP-mediated hepatic lipogenesis; *Mol Cell*

Endocrinol 2018;474:260), both of which remain abnormally low on OC, but normalize on SPIOMET treatment. The on-treatment Z-scores of fasting insulin and miR-451a explained together approximately 50% of the variation in post-treatment ovulation rates. This simple duo, if validated in larger and more diverse PCOS populations, may become a first on-treatment predictor of post-treatment ovulation rate.

Adrenal

ADRENAL PHYSIOLOGY AND DISEASE

A Novel Glucocorticoid Receptor Antagonist (CORT113176) Reveals Unique Developmental and Tissue-Specific Effects in a Neonatal Rat Model of Human Prematurity

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Premature birth is a major public health problem worldwide and can lead to transient adrenal insufficiency[1,2]. The stress of premature birth includes the inability to control blood glucose and maintain normal oxygenation leading to hypoxia[3]. Corticosteroid administration enhances surfactant production and improves oxygenation in preterm humans. However, corticosteroids can also have negative consequences[4,5]. We have validated a rat model of separation and hypoxia on post-natal day (PD) 2 that emulates the stress and treatment of hypoxia in the preterm human infant[6,7]. We hypothesized that the role of endogenous glucocorticoids in our neonatal rat model of preterm birth can be evaluated using the novel selective glucocorticoid receptor (GR) antagonist CORT113176 (Corcept) which is devoid of progesterone receptor effects[8]. Pups (PD 2, 8, or 15; N=6–8 per treatment/timepoint) were given CORT113176 (60 mg/kg IP) or vehicle, then placed into chambers in room air with mild warming to prevent hypothermia due to maternal separation. 60 min later, one group of pups was euthanized and trunk blood collected (baseline). The remaining pups were exposed to hypoxia (8% O2) or normoxia (time control) for 30 or 60 min at which times trunk blood was collected for the measurement of plasma glucose, insulin, ACTH, and corticosterone. Plasma ACTH, corticosterone, and insulin were measured by immunoassay. Glucose was measured by glucose oxidase method and insulin sensitivity calculated (HOMA-IR). Organs were frozen (brain, pituitary, adrenal glands, kidney, liver, muscle, fat) for future assessment of tissue-specific glucocorticoid-sensitive gene expression. In PD2 rats, basal and hypoxia-stimulated plasma ACTH and corticosterone were lower and basal HOMA-IR greater with CORT113176 pretreatment suggesting (unexpectedly) glucocorticoid agonist activity. In PD8 and PD15 rats, basal and hypoxia-stimulated plasma ACTH and corticosterone were augmented after CORT113176 pretreatment demonstrating classic antagonist activity. However, in PD8 rats, CORT113176 effects were tissue-specific acting as a classic antagonist on the HPA-axis, but as an agonist on whole-body insulin resistance. The differential effects of CORT113176 based on age and target tissue indicate that GR regulation changes in early development in our animal model of human prematurity. These findings may have significant implications in the treatment of hypoxia and transient adrenal insufficiency in the preterm infant[1,2] as well as give insight into the nuances of the control of glucocorticoid receptor function.

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Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS

Use of ACTH-Stimulated Lateralization Indices Underestimates Surgically Curable Primary Aldosteronism

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Introduction: Adrenal venous sampling (AVS) is recommended to assess laterality in primary aldosteronism to determine whether a patient has unilateral, or surgically curable, disease. Institutional practices differ in whether ACTH stimulation is used or not and if so, whether values are obtained after a single injection of ACTH or during an ACTH infusion. Studies have demonstrated appreciable discordance between lateralization based on unstimulated versus stimulated AVS.

Objective: To assess the influence of ACTH-stimulation on lateralization indices.

Methods: We performed a retrospective cross-sectional analysis of 140 patients who underwent AVS between 2012–2019. We then validated these findings in a separate cohort of 233 patients who underwent AVS between 2008–2016. AVS was performed using simultaneous, unstimulated, and triplicate sampling from the inferior vena cava (IVC) and bilateral adrenal veins, followed by repeated sampling in duplicate or triplicate from each site following a bolus of 250 ug of ACTH (cosyntropin). The lateralization index (LI) was defined as the quotient of the aldosterone-to-cortisol ratios from each adrenal vein, and the categorical definition of lateralization was defined as a LI ≥ 2 (unstimulated) and LI ≥ 4 post-ACTH.

Results: The median unstimulated LI was 8.7 compared to 8.9 post-ACTH. Seventy-one of 140 patients (51%) had a decrease in LI following the ACTH bolus. Overall lateralization discordance was 21.4%, with the majority of this discordance (90%) attributed to situations where there was an unstimulated LI ≥ 2 that became a post-ACTH LI < 4, thereby transforming a unilateral interpretation into one of bilateral disease. Comparing the group that had an