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Background: Secondary adrenal insufficiency (AI) can develop following unilateral adrenalectomy (UA) foradrenal-dependent hypercortisolism (HC) and has been reported after UA for primaryaldosteronism (PA). An institutional study previously demonstrated that cosyntropin stimulationtesting on postoperative day 1 (POD1-CST) successfully identified patients who requiredglucocorticoid replacement (GR) following UA; 50% of HC patients required GR and no PApatients required GR. The aim of this study was to reevaluate the need for GR following UA forpatients with HC and PA in a larger cohort of patients. Methods We reviewed 108 patients from a prospectively maintained adrenal database who underwent UAfor HC (n=74), PA (n=22), and concurrent HC/PA (n=12) from 9/2014-10/2020. PA patientswithout preoperative evaluation for HC were excluded. Patients with 1mg dexamethasonesuppression test (DST) cortisol >1.8 (μg/dL) were defined as having mild HC, with ³5 defined asovert Cushing's Syndrome (CS). All patients underwent our institutional POD1-CST protocoland GR was initiated for patients with basal cortisol £5 or stimulated cortisol £14 (<18 prior to4/2017). **Results:** Overall, 51 (47%) patients had an abnormal POD1-CST and were discharged on GR (44 HC, 1PA, and 6 HC/PA). Two (2%) patients with CS had a normal POD1-CST but developed AIrequiring GR at 8 and 12 weeks post UA. Of the 74 patients with HC, 44 (59%) had an abnormalPOD1-CST and were discharged on GR, including 19/28 (68%) with CS and 25/46 (54%) withmild HC. Preoperative DST cortisol was higher in HC patients who required GR compared topatients with a normal POD1-CST (4.1 vs 3.6; p=0.007). Median cortisol levels for HC patientswith an abnormal POD1-CST vs those with a normal test were: basal: 3.8 vs 15.6 (p=0.027); 30-minute: 10.1 vs 20.1 (p=0.403); and 60-minute 11.4 vs 22.2 (p=0.260). Of the 22 PA patients, 19(86%) had a normal POD1-CST. Median cortisol levels for PA patients with an abnormal POD1-CST vs those with a normal test were: basal: 0.4 vs 12.1; 30-minute: 8.8 vs 24.6; and 60-minute:12.2 vs 28.9. Of the 3 (14%) PA patients with an abnormal POD1-CST, 1 was dischargedwith GR and began tapering after 2 weeks; the other 2 did not require GR and did not developAI. Of the 12 patients with combined PA/HC, 6 (50%) were discharged on GR based on POD1-CST. GR was required by 30 (59%) patients for <3 months and 82% for <12 months; 7/9 whorequired GR >12 months had CS. **Conclusions:** Using a standard protocol for POD1-CST in patients who underwent unilateral adrenalectomyfor HC, PA, or combined PA/HC, this study demonstrated that routine GR is not required in 32%of patients with CS and 46% of patients with mild HC. POD1-CST safely identifies patients whowill require GR with no immediate concern for adrenal insufficiency. These data also suggestthat routine evaluation for AI in postoperative PA patients is not needed if cortisol excess hasbeen excluded preoperatively.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Cortisol Levels Is Associated With Left Ventricular Diastolic Dysfunction in Diabetic Patients

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Introduction: Diabetes mellitus (DM) is a major cause of cardiovascular disease including heart failure with preserved ejection fraction (HFpEF), which is characterized by left ventricular diastolic dysfunction (LVDD). It is reported that Cushing's syndrome is also associated with LVDD. The relationship between plasma cortisol concentration and LVDD, however, has not been investigated in patients with DM. **Methods:** In this study, 109 patients with DM and 104 patients with non-DM without overt heart failure were enrolled. Left ventricular function were assessed using echocardiography. The ratio of early diastolic velocity (E) from transmitral inflow to early diastolic velocity (e') of tissue Doppler at mitral annulus (E/e') was used as an index of diastolic function. Parameters of plasma cortisol concentration, glycemic control, lipid profile, treatment with anti-diabetic drugs and other clinical characteristics were evaluated, and their association with E/e' determined. Patients taking steroids, undergoing dialysis treatment and with overt heart failure were excluded. **Results:** Univariate analysis showed that E/e' was significantly correlated with age (p<0.001), duration of diabetes (p=0.039), systolic blood pressure (SBP) (p<0.001), eGFR (p=0.002), sodium glucose cotransporter 2 (SGLT2) inhibitor use (p<0.001) and cortisol (p=0.009) in patients with DM. Multivariate linear regression analysis showed that log E/e' was positively correlated with age (p=0.018), log SBP (p= 0.005), eGFR (p=0.015), cortisol (p=0.028) and that log E/e' was inversely with inhibitor use (p=0.018). There was no association between E/e' and cortisol in patients with non-DM. **Conclusions:** Cortisol may be important in the development of LVDD in patients with DM.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Deliberate Compensated Vasoplegia - a Novel Pharmacological Regimen for Controlling Arterial Blood Pressure During Surgery for Pheochromocytoma

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Background: Intraoperative hemodynamic fluctuations are the most dreaded phenomenon associated with the treatment of pheochromocytoma. Preoperative alpha-adrenergic blockade protocols aimed at abating these fluctuations have achieved controversial results. No study to date has evaluated the use of intraoperative treatment protocols during surgery for pheochromocytoma. Deliberate compensated vasoplegia (DCV) is a novel pharmacological regimen developed at our institution intended to decrease

severe hypertensive events. The aim of this study is to compare outcomes of pheochromocytoma resection with and without the DCV protocol. **Methods:** A retrospective analysis of all pheochromocytoma resections between the years 2012 and 2020 was performed. Resections performed with and without the DCV protocol were compared. The primary outcome measured was the incidence of severe intraoperative hypertension (mean arterial pressure ≥ 150 mmHg). Secondary outcomes included other abnormal blood pressure measurements as well as perioperative data and complications. **Results:** A total of 41 pheochromocytoma resections were included: 21 performed using standard practice and 20 with the DCV protocol. Analysis demonstrated no significant difference in preoperative parameters including tumor size, catecholamine levels, or alpha-blockade protocol. The use of the DCV protocol resulted in a significant decrease in the incidence of severe hypertensive episodes from 1.95±3.6 to 0.03±0.13 events/hour (p=0.008). The DCV protocol was not associated with any adverse events. **Conclusions:** This study demonstrates that DCV anesthesia protocol significantly decreases the incidence of severe hypertensive episodes during pheochromocytoma resection. This is the first study describing a highly effective protocol for controlling intraoperative hypertension and hemodynamic instability in pheochromocytoma patients.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Design of a Phase 1/2 Open-Label, Dose-Escalation Study of the Safety and Efficacy of Gene Therapy in Adults With Classic Congenital Adrenal Hyperplasia (CAH) Due to 21-hydroxylase Deficiency Through Administration of an Adeno-Associated Virus (AAV) Serotype 5-Based Recombinant Vector Encoding the Human CYP21A2 Gene

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The *CYP21A2* gene, which encodes the 21-hydroxylase enzyme, plays a critical role in glucocorticoid (GC) and mineralocorticoid synthesis by the adrenal cortex. *CYP21A2* pathogenic variants cause 21-hydroxylase deficiency (21OHD), the most common type of CAH, characterized by variable degrees of adrenal insufficiency and androgen excess. Standard treatment of classic 21OHD consists of daily doses of GC and mineralocorticoid. However, suppressive GC doses are often required to reduce androgen excess, and it is often not possible to dose exogenous GC in a manner that provides adequate disease control while avoiding overtreatment. Disease-related and treatment-related comorbidities are common and include life-threatening adrenal crises, impaired growth and development during childhood, adult short stature, virilization in females, subfertility in both sexes, obesity and cardiovascular risk factors, and decreased bone mineral density. Novel treatment approaches are needed to address these challenges and a treatment that restores the ability of the adrenals to produce cortisol and aldosterone in a physiologically-regulated manner would be particularly helpful.

Here we present the design and rationale of a clinical trial using BBP-631, an AAV5 gene replacement therapy for adults with classic CAH due to 21-OHD. This treatment approach is based on the demonstration that a single intravenous administration of BBP-631 corrects the enzyme deficiency in the H2-aw18 *CYP21-/-* CAH mouse model of 21OHD, including response to stress. This correction was robust, dose-dependent and durable. BBP-631 treatment also resulted in robust and durable expression of the human *CYP21A2* transgene in the non-human primate adrenal cortex. BBP-631 appears to be safe and well-tolerated in mice with 21-OHD, healthy mice and non-human primates. Taken together, these data support initiating clinical trials in adults with classic CAH due to 21-OHD.

The trial will sequentially enroll individuals in up to 3 successive dose-escalation cohorts. Each subject will receive a single dose of BBP-631 and safety will be assessed prior to dose escalation. Endogenous production rates of adrenal steroids (cortisol, 17-hydroxyprogesterone, androstenedione) will be determined pre- and post- dose, and their concentrations assessed over a 1-year period after which subjects will roll over into an extension study for at least 4 years. The Phase 1 study will determine the tolerability of a single dose of BBP-631. The magnitude and durability of BBP-631 and effects on adrenal steroids, ACTH and, where relevant, aldosterone levels will be monitored. The ability of BBP-631 to allow tapering of GC doses will also be explored. This first in human study of gene therapy for CAH represents a milestone in the development of novel and improved treatment approaches for patients with classic CAH.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Development of Deep Learning-Based Automatic Detection Algorithm for Adrenal Nodules on Contrast-Enhanced Abdominal CT Scans

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Objective: Adrenal nodules are often incidentally detected on abdominal computed tomography (CT) scans due to their asymptomatic nature. We aimed to develop an automatic detection program for adrenal nodules on abdominal CT scans using deep learning algorithms. **Methods:** We