Adrenal

ADRENAL - HYPERTENSION

Phaeochromocytoma-Paraganglioma (PPGL): Post-Operative Hypotension Is a Vanishing Phenomenon

Esther Osher, MD PhD; Karen Michele Tordjman, MD; Joseph Klausner, MD; Ido Nachmany, MD; Boaz Sagie, MD; Naftali Stern, MD; Guy Lahat, MD; Ido Wolf, MD; Lilach Zac, MD; Sorina Otremski, MD; Sophie Barnes, MD; asaf Aizin, MD; Naomi Even Zohar, MD PhD; Yona Greenman, MD.

1Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel, Tel-Aviv, Israel, 2Department of Surgery, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel, Tel-Aviv, Israel, 3Department of Oncology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel, Tel-Aviv, Israel, 4Department of Anesthesiology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel, Tel-Aviv, Israel, 5Department of Radiology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel, Tel-Aviv, Israel, 6Department of Pathology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel, Tel-Aviv, Israel.

MON-194 Background: Treatment of hemodynamic instability in patients with PPGL in the intra-and postoperative periods is challenging. Persistent postoperative hypotension is a common and serious complication, reportedly occurring in 30-60% of PPGL patients. This phenomenon reflects 1) high doses of pre-operative antihypertensive drugs; 2) low intravascular volume secondary to chronic catecholamine-induced vasoconstriction with pressure natriuresis; 3) the sudden drop in circulating catecholamines after surgery. It has been shown that tumor size and preoperative levels of catecholamines are directly related to the need for treatment with vasopressor agents in the early period after tumor removal. The aim of this study was to evaluate the efficacy and safety of the current perioperative treatment protocol for PPGL used in our Institute. Methods: We retrospectively reviewed the rate of hemodynamic instability and postoperative hypotension in relation to catecholamine levels, and the efficiency of preoperative pharmacological preparation in consecutive patients with PPGL treated between 2000-2019. Results: There were 39 patients (F/M 19/20; mean age 50.4 ±16.5 years) 33 of which had adrenal lesions and 6 had extra-adrenal tumors. Mean tumor size was 3.9 ±2.2 cm. Median metanephrine and normetanephrine levels were 5 and 10 fold the upper limit of the normal range respectively. All patients were treated with α-blockade (phenoxybenzamine-17, mean dose 60±38 mg/day; doxazosin-22; mean dose 9.6±6.1mg/day) along with β-blockade, and high sodium diet and IV saline 24 hours before the operation. The length of the preoperative preparation period was 3±2 weeks. Within the first 24-48 hours from surgery, no episodes of hypotension (<90 mmHg systolic pressure) were recorded. Mean systolic BP was 121 ±14 (range 95-150) with a mean diastolic BP of 70 ±11 (range 89-46). In contrast, intraoperative hypotension occurred in 22% of the patients; and BP surge occurred in 36% of patients, mostly during tumor manipulation. There were no differences between subjects with and without such BP rises/falls in terms of pre/post- surgical BP, catecholamine levels or type of medical treatment. Conclusion: In contrast with older literature and previous reports, the patients in our cohort did not experience postoperative hypotension. This is most likely due to tight BP control while avoiding pre-operative hypotension, and adequate volume control. We propose that proper pre-operative management in the modern era can drastically minimize intraoperative hemodynamic instability and post-operative hypotension.

Reproductive Endocrinology

MALE REPRODUCTIVE HEALTH - FROM HORMONES TO GAMETES

Ambulatory Blood Pressure Increases in Hypogonadal Men Who Develop Increases in Hematocrit on Oral Testosterone Undecanoate

Adrian Sandra Dobs, MD, MHS; William B. White, MD, Culley Carson, MD; Anthony DelConte, MD; Mohit Khera, MD, MBA, MPH; Martin Miner, MD; Muhama Shahid, BS; Konnara Papangkorn, PhD; Kilyoung Kim, PhD; Nachiappan Chidambaram, PhD.

1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2University of Connecticut Health Center, Farmington, CT, USA, 3University of North Carolina School of Medicine, Chapel Hill, NC, USA, 4Saint Joseph’s University, Philadelphia, PA, USA, 5Baylor College of Medicine Medical Center, Houston, TX, USA, 6Men’s Health Center The Miriam Hotel, Providence, RI, USA, 7Lipocine Inc, Salt Lake City, UT, USA.

SAT-038 There is concern that testosterone replacement therapies might increase blood pressure (BP) with chronic use.
Testosterone undecanoate is a novel oral testosterone therapy under development for the treatment of male hypogonadism. We studied the effects of testosterone undecanoate (225 mg twice daily) on ambulatory blood pressure (ABP) and heart rate, in 138 men with hypogonadism (mean age, 54 years, 79% white, 48% with a history of hypertension). Ambulatory BP and heart rate and hematologic parameters were obtained at baseline and following 4 months of daily therapy. Changes from baseline in ambulatory 24-hour, awake, and sleep systolic BP of 3.8 (p=0.06), 5.2 (p=0.01), and 4.3 mmHg (p=0.07) were observed post-treatment, respectively. Smaller changes in the diastolic BP were observed (1.2 (p=0.13), 1.7 (p=0.04), and 1.7 mmHg (p=0.11) for 24-hour, awake, and sleep, respectively). Changes in the 24-hour, awake and sleep heart rates were 1.9 (p=0.07), 2.6 (p=0.02), and 0.4 (p=0.68) beats/minute respectively. There were no significant differences in changes from baseline in the 24-hour ambulatory BP for the 57 subjects who had a medical history of hypertension versus the 61 subjects who did not have hypertension: 4.5/1.5 mmHg in the hypertension subgroup versus 3.2/0.9 mmHg in the non-hypertensive subgroup (p = 0.53/0.46 between groups). Hematocrit and hemoglobin increased by 3.2% and 0.9 g/dl in all subjects after 4 months of therapy. In those men in the top quartile of changes in hematocrit (corresponding to upper / lower boundary changes of 6 and 14% with 9.3% achieving levels > 52%), the largest increases in ambulatory systolic BP (8.3 mmHg) were observed, whereas the changes in ambulatory systolic BP in the lower 3 quartiles were substantially smaller (1.6, 3.2, and 2.7 mmHg in quartiles 1, 2 and 3 of hematocrit change, respectively). In conclusion, these data demonstrate increases in ambulatory BP occurred following 4 months of oral testosterone undecanoate, particularly in those men whose hematocrit rose by > 6% or whose resultant hematocrit was 52% or higher. Hence, hematocrit maybe a useful clinical parameter that could effectively predict the risk of developing increases in BP on oral testosterone undecanoate.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Regulation of Low-Density Lipoprotein Receptor Expression in Triple Negative Breast Cancer

Tiffany Scully, PhD, Nathan G. Kase, MD, Emily Jane Gallagher, MB,BCh,BAO, PhD, Derek LeBoith, MD,PHD.

Icahn School of Medicine at Mount Sinai, New York, NY, USA.

SAT-151

Preclinical models and clinical studies suggest that hypercholesterolemia promotes breast cancer progression.1,2 The expression of the low-density lipoprotein receptor (LDLR) has been positively associated with poorer recurrence-free survival in human breast cancer studies.3 Mechanistically, LDLR has been demonstrated to play a role in the increased tumor growth associated with hypercholesterolemia, as knock-down of LDLR led to decreased tumor growth in setting of elevated circulating LDL cholesterol. The aim of this study was to identify factors which up-regulate expression of LDLR in triple negative breast cancer (TNBC).

In glioblastoma, hyper-activation of the epidermal growth factor receptor (EGFR) signaling pathway has been associated with greater LDLR expression and susceptibility to targeting of cholesterol metabolism.4 As EGFR is frequently expressed in TNBC, we examined if increased LDLR expression is associated with activation of the EGFR signaling pathway in TNBC. The expression of LDLR in the TNBC cell lines, MDA-MB-231 (231) and MDA-MB-468 (468) was examined pre- and post-EGF stimulation of the EGFR and in the presence of chemical inhibitors. Cells were grown in DMEM/10% FBS/1% Pen/strep (P/S), and experiments were performed under reduced serum conditions at 1.25%FBS/DMEM/1%P/S. In the absence of stimulation, LDLR protein expression was 3-fold higher in 231 vs 468 cell lines. This was despite mRNA expression being comparable at baseline, suggesting that the difference in protein expression was post-transcriptionally mediated. Treatment with 10 ng/mL EGF for 2 hours led to an increased activation of the EGFR, phosphorylation of Akt and extracellular signal regulated kinase (ERK) in both cell lines but induced an increase in LDLR protein and mRNA expression only in 468 cells. Treatment of 468 cells with EGF after exposure to actinomycin, a transcription inhibitor, revealed that EGF treatment resulted in reduced degradation of LDLR mRNA (p = 0.002) over 3 hours, suggesting that the EGF-induced increase in LDLR expression was by protection of LDLR mRNA from degradation. Chemical inhibition of the ERK pathway with 20 μM U0126 reduced both the EGF-induced increase in LDLR expression in 468 cells (p = 0.015) as well as the high baseline expression of LDLR by half in 231 cells (p = 0.001). Overall our results suggest that the EGFR/ERK signaling pathway regulates LDLR expression in TNBC, supporting the increased anabolic needs of this aggressive, swiftly expanding form of breast cancer.

References: 1Alikhani, N. et al., Oncogene 32, 961-967 (2013), 2Pelton, K. et al., Am. J. Pathol. 184, 2099-2110 (2014), 3Gallagher, E. J. et al., Oncogene 36, 6462-6471 (2017), 4Guo, D. et al., Cancer Discov. 1, 442-456 (2011), 5Reis-Filho, J. S. & Tutt, A. N. J. Histopathology 52, 108-118 (2008).

Reproductive Endocrinology

FEMALE REPRODUCTION: BASIC MECHANISMS

Maternal Behaviour in Mice Is Modified by a High Fat Diet in Pregnancy

Showall Moazzam, Noshin Noorjahan, Jessica S. Jarmaz, PhD, Yan Jin, Tabrez J. Siddiqui, PhD, Peter Andrew Cattini, PhD.

University of Manitoba, Winnipeg, MB, Canada.

MON-019

Background: About a third of pregnant women of age 20-39 are obese, which carries significant risks for the mother and fetus, and adversely impacts pregnancy outcome. Specifically, women with obesity are at increased risk for peripartum depression. Maternal behaviour in mice is influenced by changes in hormone signaling in pregnancy, which is associated with effects on adult neurogenesis in the brain. Thus, we used mouse as a model system to gain further insight into the possible relationship between overeating/obesity and brain physiology and maternal...