El material que se presenta a continuación proviene de los datos proporcionados por la OAIC (Oficina de Apoyo a la Investigación Clínica de nuestro Hospital) así como de la que nos facilitaron los servicios en respuesta a nuestra solicitud en diciembre del 2010.

Abstracts de publicaciones internacionales ISI 2010

DEPARTAMENTO DE ANATOMÍA PATOLÓGICA

PATHOL RES PRACT. 2010 NOV 15;206(11):788-91.

ADULT VARIANT OF ATYPICAL TERATOID/RHABDOID TUMOR: IMMUNOHISTOCHEMICAL AND ULTRASTRUCTURAL CONFIRMATION OF A RARE TUMOR IN THE SELLA TURSICA.

Las Heras F, Pritzker KP.

Atypical teratoid/rhabdoid tumor (AT/RT) is a distinctive neoplasm of young children characterized by diverse histology and fatal course. Adult presentation is rare. We describe the diagnostic problems associated with an AT/RT arising in the sellar region in a 46-year-old female. Vimentin, keratin, synaptophysin, CD34, SMA, PLAP, GFAP, S-100, NSE, desmin, MYF-4, LCA, and CD99 were performed on tissue obtained from the paraffin block. INI1 protein expression was immunohistochemically determined on tumor tissue. Electron microscopy was performed from the tissue block. The tumor was composed of large atypical "rhabdoid" cells having macronucleoli and abundant eosinophilic cytoplasm. Immunohistochemistry showed that the tumor cells were positive for vimentin, CD34, CD99, and reacted variably for keratin, synaptophysin, NSE, and SMA. All were negative for GFAP, S-100, desmin, MYF-4, and LCA. The tumor cells lacked nuclear expression of INI1. Electron microscopy revealed cells with large paranuclear intracytoplasmic collections of intermediate filaments. AT/RT should be considered when dealing with a malignant neoplasm with rhabdoid features, regardless of age. Immunohistochemistry is of importance in differentiating this entity from primitive neuroectodermal tumors (PNET) and carcinosarcomas. Lack of nuclear INI1 protein expression by immunohistochemical methods is required for a reliable diagnosis.

BRITISH JOURNAL OF CANCER 2010 OCT 12;103(8):1277-83.

ARSENIC-RELATED DNA COPY-NUMBER ALTERATIONS IN LUNG SQUAMOUS CELL CARCINOMAS.

VD Martinez, TPH Buys, M Adonis, H Benítez, **I Gallegos**, S Lam, WL Lam and L Gil.

BACKGROUND: Lung squamous cell carcinomas (SqCCs) occur at higher rates following arsenic exposure. Somatic DNA copy-number alterations (CNAs) are understood to be critical drivers in several tumour types. We have assembled a rare panel of lung tumours from a population with chronic arsenic exposure, including SqCC tumours from patients with no smoking history. METHODS: Fifty-two lung SqCCs were analysed by whole-genome tiling-set array comparative genomic hybridisation. Twenty-two were derived from arsenic-exposed patients from Northern Chile (10 never smokers and 12 smokers). Thirty additional cases were obtained for comparison from North American smokers without arsenic exposure. Twenty-two blood samples from healthy individuals from Northern Chile were examined to identify germline DNA copy-number variations (CNVs) that could be excluded from analysis. RESULTS: We identified multiple CNAs associated with arsenic exposure. These alterations were not attributable to either smoking status or CNVs. DNA losses at chromosomes 1q21.1, 7p22.3, 9q12, and 19q13.31

represented the most recurrent events. An arsenic-associated gain at 19q13.33 contains genes previously identified as oncogene candidates. CONCLUSIONS: Our results provide a comprehensive approach to molecular characteristics of the arsenic-exposed lung cáncer genome and the non-smoking lung SqCC genome. The distinct and recurrent arsenic-related alterations suggest that this group of tumours may be considered as a separate disease subclass.

GASTROENTEROL HEPATOL. 2011 JAN;34(1):10-5.

[HISTOLOGICAL REGRESSION OF LIVER FIBROSIS WITH IMMUNOSUPPRESSIVE THERAPY IN AUTOIMMUNE HEPATITIS].

Valera JM, **Smok G,** Márquez S, **Poniachik J, Brahm J.**

Reversibility of liver fibrosis with immunosuppressive therapy (IT) has been described in autoimmune hepatitis (AIH). OBJECTIVE: To compare initial fibrosis and fibrosis after IT in patients with AIH. METHODS: A total of 54 patients were admitted with positive ANA or AML antibodies, or both, elevated IgG immunoglobulins and who met international criteria for a diagnosis of AIH. The mean age was 39 years (range 13-65) and there were 47 women (87%). Two liver biopsies were taken: one at diagnosis and another at a mean of 28±8 months after initiation of IT with prednisone and azathioprine. The degree of inflammation (0-18) and fibrosis (0-6) according to Ishak score was compared between the initial and the follow-up biopsy. RESULTS: Fibrosis decreased from 2.9±0.3 to 2.2±0.3 (p=0.005) and histological activity index from 6.8±0.45 to 2.6±0.2 (P<.001). In subgroups, fibrosis decreased from 3.6±0.4 to 1.4±0.3 (P<.001) in 22 patients (41%), was unchanged in 27 (50%) and increased in five (9%). There were seven patients with histological cirrhosis at IT initiation. After IT, four showed a reduction in Ishak score (achieving scores of 0-3). Transaminase values were not associated with histological improvement. CONCLUSION: Fibrosis in patients with AIH significantly improved with IT, emphasizing the importance of studying the prognostic factors associated with this favorable response.

APPL IMMUNOHISTOCHEM MOL MORPHOL. 2010 SEP 28.

IMMUNOHISTOCHEMISTRY EXPRESSION OF P53, KI67, CD30, AND CD117 AND PRESENCE OF CLINICAL METASTASIS AT DIAGNOSIS OF TESTICULAR SEMINOMA.

Gallegos I, Valdevenito JP, Miranda R, **Fernandez C**.

INTRODUCTION: We evaluated the immunohistochemical expression of p53, Ki67, CD30, and CD117 and correlated it with histological features and presence of clinical metastasis at diagnosis of testicular seminomas. MATERIALS AND METHODS: A retrospective study of 62 patients was performed in patients with pure seminoma. The retroperitoneum was staged with computed tomography scan and the thorax with simple x-rays and/or computed tomography scan. Pathologists were unaware of the clinical stage of the patients. Manual microarrays were created from a tissue representative of tumor. The expression of p53, Ki67, CD30, and CD117 was evaluated as negative, any degree of expression, and expression in more than 50% of neoplastic cells. Univariate and multivariate analysis were performed. RESULTS: Sixty-two cases were analyzed: 43 cases were in clinical stage I (69.4%), 17 were in clinical stage II (27.4%), and 2 were in clinical stage III (3.2%). Fifty-six cases expressed CD117 (90%), 42 p53 (68%), 8 CD30 (13%), and all cases Ki67. There were no differences in p53, Ki67, CD30, and CD117 expression between testicular seminoma with and without clinical metastasis at diagnosis, regardless of the magnitude of expression. Neither of them found positive association between these marker expressions and morphologic risk factors such as tumor size greater than 6 cm and rete testis invasion. CONCLUSIONS: This study shows that expression of p53, Ki67, and CD30 and loss of CD117 expression fail to predict the presence of clinical metastasis at diagnosis of testicular seminoma and do not correlate with other histopathological risk factors in clinical stage I patients.

UROLOGIC ONCOLOGY: SEMINARS AND ORIGINAL INVESTIGATIONS 28 (2010) 534–540.

THE EXPRESSION OF SYNDECAN-1 AND -2 IS ASSOCIATED WITH GLEASON SCORE AND EPITHELIAL-MESENCHYMAL TRANSITION MARKERS, E-CADHERIN AND B-CATENIN, IN PROSTATE CANCER.

Hector R. Contreras, Rodrigo A. Ledezma, Jorge Vergara, Federico Cifuentes, Cristina Barra, Pablo Cabello, **Ivan Gallegos**, Bernardo Morales, **Christian Huidobro**, Enrique A. Castellón.

The epithelial-mesenchymal transition (EMT) is considered a key step in tumor progression, where the invasive cancer cells change from epithelial to mesenchymal phenotype. During this process, a decrease or loss in adhesion molecules expression and an increase in migration molecules expression are observed. The aim of this work was to determine the expression and cellular distribution of syndecan-1 and -2 (migration molecules) and E-cadherin and β-catenin (adhesion molecules) in different stages of prostate cancer progression. A quantitative immunohistochemical study of these molecules was carried out in tissue samples from benign prostatic hyperplasia and prostate carcinoma, with low and high Gleason score, obtained from biopsies

archives of the Clinic Hospital of the University of Chile and Dipreca Hospital. Polyclonal specific antibodies and amplification system of estreptavidin-biotin peroxidase and diaminobenzidine were used. Syndecan-1 was uniformly expressed in basolateral membranes of normal epithelium, changing to a granular cytoplasmatic expression pattern in carcinomas. Syndecan-2 was observed mainly in a cytoplasmatic granular pattern, with high immunostaining intensity in areas of low Gleason score. E-cadherin was detected in basolateral membrane of normal epithelia showing decreased expression in high Gleason score samples. β-catenin was found in cell membranes of normal epithelia changing its distribution toward the nucleus and cytoplasm in carcinoma samples. We concluded that changes in expression and cell distribution of E-cadherin and β-catenin correlated with the progression degree of prostate adenocarcinoma, suggesting a role of these molecules as markers of progression and prognosis. Furthermore, changes in the pattern expression of syndecan-1 and -2 indicate that both molecules may be involved in the EMT and tumor progression of prostate cancer.

DEPARTAMENTO DE ANESTESIOLOGÍA Y REANIMACIÓN

J MOL CELL CARDIOL. 2010 AUG;49(2):271-9.

CALPAIN TRANSLOCATION AND ACTIVATION AS PHARMACOLOGICAL TARGETS DURING MYOCARDIAL ISCHEMIA/ REPERFUSION.

Hernando V, Inserte J, Sartório CL, **Parra VM,** Poncelas-Nozal M, Garcia-Dorado D.

Calpains contribute to reperfusion-induced myocardial cell death. However, it remains controversial whether its activation occurs during ischemia or reperfusion. We investigated the regulation and time-course of calpain activation secondary to transient ischemia and the efficacy of its inhibition at reperfusion as a therapeutic strategy to limit infarct size. In isolated rat hearts (Sprague-Dawley), ischemia induced a time-dependent translocation of m-calpain to the membrane that was not associated with calpain activation as assessed by proteolysis of its substrate alpha-fodrin. Translocation of calpain was dependent on Ca(2+) entry through reverse mode Na(+)/Ca(2+)-exchange and was independent of acidosis. Calpain activation occurred during reperfusion, but only after intracellular pH (pHi) normalization, and was not prevented by inhibiting its translocation during ischemia with methyl-beta-cyclodextrin. The intravenous infusion of MDL-28170 in an in vivo rat model with transient coronary occlusion during the first minutes of reperfusion resulted in a reduction of infarct size (43.9+/-3.9% vs. 60.2+/-4.7, P=0.046, n=18) and alpha-fodrin degradation. These results suggest that (1) Ca(2+)-induced calpain translocation to the membrane during ischemia is independent of its activation, (2) intracellular acidosis inhibits calpain activation during ischemia and pHi normalization allows activation upon reperfusion, and (3) calpain inhibition at the time of reperfusion appears as a potentially useful strategy to limit infarct size

BR J ANAESTH. 2010 OCT;105(4):448-56.

INFLUENCE OF OBESITY ON PROPOFOL PHARMACOKINETICS: DERIVATION OF A PHARMACOKINETIC MODEL.

Cortínez LI, Anderson BJ, **Penna A**, Olivares L, Muñoz HR, Holford NH, Struys MM, Sepulveda P.

BACKGROUND: The objective of this study was to develop a pharmacokinetic (PK) model to characterize the influence of obesity on propofol PK parameters. METHODS: Nineteen obese ASA II patients undergoing bariatric surgery were studied. Patients received propofol 2 mg kg(-1) bolus dose followed by a 5-20-40-120 min, 10-8-6-5 mg kg(-1) h(-1) infusion. Arterial blood samples were withdrawn at 1, 3, 5 min after induction, every 10-20 min during propofol infusion, and every 10-30 min for 2 h after stopping the propofol infusion. Arterial samples were processed by high-performance liquid chromatography. Time-concentration data profiles from this study were pooled with data from two other propofol PK studies available at http://www.opentci.org. Population PK modelling was performed using non-linear mixed effects model. RESULTS: The study involved 19 obese adults who contributed 163 observations. The pooled analysis involved 51 patients (weight 93 sd 24 kg, range 44-160 kg; age 46 sd 16 yr, range 25-81 yr; BMI 33 sd 9 kg m(-2), range 16-52 kg m(-2)). A three-compartment model was used to investigate propofol PK. An allometric size model using total body weight (TBW) was superior to all other models investigated (linear TBW, free fat mass, lean body weight, normal fat mass) for all clearance parameters. Variability in V2 and Q2 was reduced by a function showing a decrease in both parameters with age. CONCLUSIONS: We have derived a population PK model using obese and non-obese data to characterize propofol PK over a wide range of body weights. An allometric model using TBW as the size descriptor of volumes and clearances was superior to other size descriptors to characterize propofol PK in obese patients.

J CARDIOVASC PHARMACOL. 2010 SEP;56(3):268-74.

LATE CARDIAC PRECONDITIONING BY EXERCISE IN DOGS IS MEDIATED BY MITOCHONDRIAL POTASSIUM CHANNELS.

Parra VM, Macho P, Domenech RJ.

We previously showed that exercise induces myocardial preconditioning in dogs and that early preconditioning is mediated through mitochondrial adenosine triphosphate-sensitive potassium channels. We decided to study if late preconditioning by exercise is also mediated through these channels. Forty-eight dogs, surgically instrumented and trained to run daily, were randomly assigned to 4 groups: (1) Nonpreconditioned dogs: under anesthesia, the coronary artery was occluded during 1 hour and then reperfused during 4.5 hours. (2) Late preconditioned dogs: similar to group 1, but the dogs run on the treadmill for 5 periods of 5 minutes each, 24 hours before the coronary occlusion. (3) Late preconditioned dogs plus 5-hydroxydecanoate (5HD): similar to group 2, but 5HD was administered before the coronary occlusion. (4) Nonpreconditioned dogs plus 5HD: similar to group 1, but 5HD was administered before the coronary occlusion. Infarct size (percent of the risk region) decreased by effect of exercise by 56% ($P < 0.05$), and this effect was abolished with 5HD. 5HD by itself did not modify infarct size. Exercise did not induce myocardial ischemia, and the hemodynamics during ischemia-reperfusion period did not differ among groups. These effects were independent of changes in collateral flow to the ischemic region. We concluded that late cardiac preconditioning by exercise is mediated through mitochondrial adenosine triphosphate-sensitive potassium channels.

J BIOL CHEM. 2010 MAR 5;285(10):7566-74.

P2X4 ACTIVATION MODULATES VOLUME-SENSITIVE OUTWARDLY RECTIFYING CHLORIDE CHANNELS IN RAT HEPATOMA CELLS.

Varela D, **Penna A**, Simon F, Eguiguren AL, Leiva-Salcedo E, Cerda O, Sala F, Stutzin A.

Volume-sensitive outwardly rectifying (VSOR) Cl(-) channels are critical for the regulatory volume decrease (RVD) response triggered upon cell swelling. Recent evidence indicates that H(2)O(2) plays an essential role in the activation of these channels and that H(2)O(2) per se activates the channels under isotonic isovolumic conditions. However, a significant difference in the time course for current onset between H(2)O(2)-induced and hypotonicity-mediated VSOR Cl(-) activation is observed. In several cell types, cell swelling induced by hypotonic challenges triggers the release of ATP to the extracellular medium, which in turn, activates purinergic receptors and modulates cell volume regulation. In this study, we have addressed the effect of purinergic receptor activation on H(2)O(2)-induced and hypotonicity-mediated VSOR Cl(-) current activation. Here we show that rat hepatoma cells (HTC) exposed to a 33% hypotonic solution responded by rapidly activating VSOR Cl(-) current and releasing ATP to the extracellular medium. In contrast, cells exposed to 200 microm H(2)O(2) VSOR Cl(-) current onset was significantly slower, and ATP release was not detected. In cells exposed to either 11% hypotonicity or 200 microm H(2)O(2), exogenous addition of ATP in the presence of extracellular Ca(2+) resulted in a decrease in the half-time for VSOR Cl(-) current onset. Conversely, in cells that overexpress a dominant-negative mutant of the ionotropic receptor P2X4 challenged with a 33% hypotonic solution, the half-time for VSOR Cl(-) current onset was significantly slowed down. Our results indicate that, at high hypotonic imbalances, swelling-induced ATP release activates the purinergic receptor P2X4, which in turn modulates the time course of VSOR Cl(-) current onset in a extracellular Ca(2+)-dependent manner.

DEPARTAMENTO DE CARDIOLOGÍA

BASIC CLIN PHARMACOL TOXICOL. 2010 NOV 4.

ANTIOXIDANT THERAPY REDUCES OXIDATIVE AND INFLAMMATORY TISSUE DAMAGE IN PATIENTS SUBJECTED TO CARDIAC SURGERY WITH EXTRACORPOREAL CIRCULATION.

Castillo R, Rodrigo R, Perez F, **Cereceda M, Asenjo R, Zamorano J**, Navarrete R, Villalabeitia E, Sanz J, Baeza C, Aguayo R.

Ischaemia reperfusion injury is a pathophysiological event that occurs after cardiac surgery with extracorporeal circulation. This clinical event has been associated with the induction of oxidative and inflammatory damage in atrial tissue. Here, we tested whether combined omega 3 polyunsaturated fatty acids (n-3 PUFA)-antioxidant vitamin protocol therapy reduces oxidative and inflammatory cardiac tissue damage. This trial assigned 95 either-sex patients to supplementation with n-3 PUFA (2 g/day), or matching placebo groups, 7 days before on-pump surgery. Antioxidant vitamins C (1 g/day) and E (400 IU/day) or placebo were added from 2 days before surgery until discharge. Blood and atrial tissue samples were obtained during the intervention. Reduced/oxidized glutathione (GSH/GSSG) ratio, malondialdehyde (MDA) and protein carbonylation

were determined in atrial tissue. Leucocyte count and high-sensitivity C-reactive protein (hs-CRP) in blood plus nuclear factor (NF)-κappaB activation in atrial tissue served for inflammation assessment. Lipid peroxidation and protein carbonylation were 27.5 and 24% lower in supplemented patients ($p < 0.01$). GSH/GSSG ratio was 38.1% higher in supplemented patients compared with placebo ($p < 0.01$). Leucocyte count and serum hs-CRP levels were markedly lower throughout the protocol in supplemented patients ($p < 0.01$). Atrial tissue NF-κB DNA activation in supplemented patients was 22.5% lower than that in placebo patients ($p < 0.05$). The combined n-3 PUFA-antioxidant vitamin protocol therapy here proposed reduced the oxidative stress and inflammation biomarkers, in patients undergoing on-pump cardiac surgery.

INFLAMMOPHARMACOLOGY. 2010 APR;18(2):65-71.

SYNERGISM BETWEEN COX-3 INHIBITORS IN TWO ANIMAL MODELS OF PAIN.

Muñoz J, Navarro C, Noriega V, Pinardi G, Sierralta F, **Prieto JC**, Miranda HF.

OBJECTIVE AND DESIGN: The antinociception induced by the intraperitoneal coadministration in mice of combinations of metamizol and paracetamol was evaluated in the tail flick test and orofacial formalin test. METHODS: The antinociception of each drugs alone and the interaction of the combinations was evaluated by isobolographic analysis in the tail-flick and in the formalin orofacial assay of mice. RESULTS: Mice pretreated with the drugs demonstrated that the antinociception of metamizol and paracetamol is dose-dependent. The potency range on the antinocifensive responses for metamizol or paracetamol was as follows: orofacial (Phase II) > orofacial (Phase I) > tail flick. In addition, the coadministration of metamizol with paracetamol induced a strong synergistic antinociception in the algesiometer assays. Both drugs showed effectiveness in inflammatory pain. CONCLUSION: These actions can be related to the differential selectivity of the drugs for inhibition of COX isoforms and also to the several additional antinociception mechanisms and pathways initiated by the analgesic drugs on pain transmission. Since the efficacy of the combination of metamizol with paracetamol has been demonstrated in the present study, this association could have a potential beneficial effect on the pharmacological treatment of clinical pain.

INT J CARDIOL. 2010 FEB 4;138(3):221-8.

USE OF VITAMINS C AND E AS A PROPHYLACTIC THERAPY TO PREVENT POSTOPERATIVE ATRIAL FIBRILLATION.

Rodrigo R, Vinay J, **Castillo R**, **Cereceda M, Asenjo R, Zamorano J**, Araya J, **Castillo-Koch R**, Espinoza J, Larraín E.

Oxidative stress has been strongly involved in the underlying mechanism of atrial fibrillation, particularly in the arrhythmia occurring in patients undergoing cardiac surgery with extracorporeal circulation (postoperative atrial fibrillation). The ischemia/reperfusion injury thus occurring in the myocardial tissue contributes to the development of tissue remodeling, thought to be responsible for the functional heart impairment. Consequently, structural changes due to the cardiac tissue biomolecules attack by reactive oxygen and/or nitrogen species could account for functional changes in ion channels, transporters, membrane conductance, cytosolic transduction signals, and other events, all associated with the occurrence of arrhythmic consequences. The lack of success and significant side effects of anti-arrhythmic drugs have given rise to attempts aimed to develop alternative novel pharmacologic treatments. On this line, the biological properties of the antioxidant vitamins C and E suggest that they could decrease the vulnerability of the heart to the oxidative damage. Nevertheless, very few studies to assess their anti-arrhythmic effects have been reported in humans. The clinical and experimental evidence supporting the view that the pharmacological use of antioxidant vitamins could contribute to prevent postoperative atrial fibrillation is presented.

DEPARTAMENTO DE CIRUGÍA

OBES SURG. 2010 JUN;20(6):744-8.

ALCOHOL ABSORPTION MODIFICATION AFTER A LAPAROSCOPIC SLEEVE GASTRECTOMY DUE TO OBESITY.

Maluenda F, Csendes A, De Aretxabala X, Poniachik J, Salvo K, Delgado I, Rodriguez P.

BACKGROUND: The different bariatric surgery techniques that alter the digestive anatomy also modify the gastric absorption surface. Since alcohol is a substance that is mainly metabolized in the stomach, the goal of this study was to determine alcohol absorption before and after a laparoscopic sleeve gastrectomy (LSG) in the same patients. METHODS: Studies were carried out on 12 morbidly obese patients who underwent a LSG (eight men and four women). Each patient was given 3.6 ml of red wine to drink at 14% for each liter of body water mass. Alcotest values (Alcoscan Alcomate AL-6000) were measured 10 min after the wine dose had been consumed. Measurements were then repeated every 5 min until the alcohol had been completely eliminated

from the bloodstream. During the postoperatory period (median of 2.3 months), the measurement was repeated with the total dose per kg adjusted to the new water body mass. The results were measured with a nonparametric analysis for repeated samples. RESULTS: The maximum average peak of the Alcotest was 2.02 g/l during the postoperative period compared to 0.87 g/l during the preoperative period (p = 0.001 Wilcoxon). At 175 min, the blood alcohol level value reaches zero (0) in all pre-operatory patients, while after surgery, an average value of 0.26 g/l was observed (p = 0.027 Wilcoxon). After 4 h, an Alcotest average of 0.20 g/l was observed in these patients. CONCLUSION: Alcohol absorption was considerably modified after LSG with higher and longer blood alcohol values for equivalent amounts of alcohol.

WORLD J SURG. 2010 SEP;34(9):2098-102.

EVOLUTION OF TYPE 2 DIABETES MELLITUS IN NON MORBID OBESE GASTRECTOMIZED PATIENTS WITH ROUX EN-Y RECONSTRUCTION: RETROSPECTIVE STUDY.

Lanzarini E, Csendes A, Lembach H, Molina J, Gutiérrez L, Silva J.

OBJECTIVE: Bariatric surgery in morbidly obese patients with type 2 diabetes results systematically in adequate glycemic control, normalization of insulinemia, and a decrease in glycosylated hemoglobin, effects that appear early after surgery in nearly 80 to 90% of them. Possible reasons that have been discussed are a decrease in caloric consumption, weight loss, and hormonal changes at the gastrointestinal level, which could have a positive effect on glucose metabolism. Various authors have proposed the possibility of passing on this indication to diabetic patients who are overweight or are mildly obese. The purpose of this retrospective investigation was to determine the effect of total or subtotal gastrectomy with Roux-en-Y reconstruction on the metabolic control of patients with type 2 diabetes with a body mass index (BMI) < 35, operated on for reasons other than obesity. METHODS: From January 1999 to December 2007, a total of 23 diabetic patients who underwent total or subtotal gastrectomy with a gastrojejunal or esphagojejunal anastomosis with Roux-en-Y reconstruction of 60 to 70 cm length were included in this investigation. RESULTS: The group consisted of 23 patients (14 men, 9 women, average age 62.9 +/- 7.9 years, average BMI 29.1 +/- 5.1). The principal reason for gastrectomy in these patients was gastric cancer in 19 patients (82.6%). The surgical procedure was total gastrectomy in 17 cases (73.9%) and subtotal gastrectomy in 6 cases (26.1%). Postoperative follow-up was 22 months. Before surgery the mean blood glucose level was 151.4 mg/dl. Late after surgery, 15 patients (65.2%) had a fasting blood glucose <126 mg/dl and are not using medication (remission), 7 (30.4%) patients have better metabolic control with a normal blood glucose but are still taking medication (improvement), and just 1 (4.3%) patient has an altered blood glucose and uses insulin (no change). CONCLUSIONS: Gastrectomy and short Roux-en-Y limb reconstruction in type 2 diabetes patients with BMI < 35, with the patients submitted to surgery mainly for gastric cancer, correlates with remission of diabetes in 65% and improvement in 30.4%.

J PLAST RECONSTR AESTHET SURG. 2011 JAN;64(1):84-90.

FLAP SURGERY FOR PRESSURE SORES: SHOULD THE UNDERLYING MUSCLE BE TRANSFERRED OR NOT?

Thiessen FE, **Andrades P**, Blondeel PN, Hamdi M, Roche N, Stillaert F, Van Landuyt K, Monstrey S.

BACKGROUND: Musculocutaneous flaps have become the first choice in the surgical repair of pressure sores, but the indication for including muscle in the transferred flaps still remains poorly defined. This study compares outcomes after muscle and non-muscle flap coverage of pressure sores to investigate whether it is still necessary to incorporate muscle tissue as part of the surgical treatment of these ulcers. METHODS: A retrospective revision of 94 consecutive patients with ischial or sacral pressure sores operated between 1996 and 2002 was performed. Depending on the inclusion of muscle into the flap, the patients were divided in two groups: musculocutaneous flap group and fasciocutaneous flap group. Charts were reviewed for patient characteristics, ulcer features and reconstructive information. Data between groups were compared with emphasis on early (haematoma or seroma, dehiscence, infections, necrosis and secondary procedures) and late (recurrence) postoperative complications. RESULTS: A total of 37 wounds were covered with muscle and 57 wounds covered without muscle tissue. The groups were comparable in relation to age, gender, ulcer characteristics and timing for surgery. There were no significant differences in early complications between the study groups. The mean follow-up period was 3.10 ± 1.8 years (range: 0.5 to 6.7). There were no statistical differences in ulcer recurrence between the groups. The type of flap used was not associated with postoperative morbidity or recurrence in the univariate and multivariate analyses. CONCLUSIONS: The findings of this clinical study indicate that the musculocutaneous flaps are as good as fasciocutaneous flaps in the reconstruction of pressure sores, and they question the long-standing dogma that muscle is needed in the repair of these ulcers.

SURG ENDOSC. 2010 SEP;24(9):2192-6.

GALLBLADDER CANCER: ROLE OF LAPAROSCOPY IN THE MANAGEMENT OF POTENTIALLY RESECTABLE TUMORS.

De Aretxabala X, Leon J, Hepp J, **Maluenda F**, Roa I.

BACKGROUND: The aim of this study was to evaluate the role that laparoscopy plays in the management of gallbladder cancer. METHOD: From August 2005 to March 2009, 23 patients affected by gallbladder cancer detected after the study of a cholecystectomy specimen underwent laparoscopy as part of their management. RESULTS: Among the patients, 5 underwent only an exploratory laparoscopy, while 11 were converted due to the existence of dense adhesions that precluded a complete exploration. Of the patients with adhesions who underwent conversion, three were unresectable. The remainder underwent a lymphadenectomy and liver resection after conversion. Of the seven who underwent a complete laparoscopic exploration, five had a lymphadenectomy and liver resection done completely by laparoscopy while conversion was needed for two. Conversion was required due to lymphatic metastasis at the hepatic pedicle and the presence of a bile leak. Postoperative time was uneventful, with patients discharged within 3 days of the operation. CONCLUSIONS: Laparoscopy may be employed in the management of patients with early forms of gallbladder cancer undergoing reoperation. Although the presence of adhesions may result in inadequate exploration, there is a subset of patients for whom it is possible to perform a complete exam. Furthermore, laparoscopic lymphadenectomy and gallbladder bed resection is a promising technique in well-selected patients.

DIS ESOPHAGUS. 2010 APR;23(3):208-15.

INVERSED Y CARDIOPLASTY PLUS A TRUNCAL VAGOTOMY-ANTRECTOMY AND A ROUX-EN-Y GASTROJEJUNOSTOMY PERFORMED IN PATIENTS WITH STRICTURE OF THE ESOPHAGOGASTRIC JUNCTION AFTER A FAILED CARDIOMYOTOMY OR ENDOSCOPIC PROCEDURE IN PATIENTS WITH ACHALASIA OF THE ESOPHAGUS.

Braghetto I, Korn O, Cardemil G, Coddou E, **Valladares H**, Henriquez A.

Laparoscopic anterior cardiomyotomy in addition to anterior Dor's fundoplication is the procedure of choice for achalasia of the esophagus with approximately 95% success rate. Redo cardiomyotomy is complicated and associated with rerecurrence of dysphagia. Twelve patients with failed redo myotomy were clinically evaluated with radiology, endoscopy, and manometry in whom achalasia type III or IV was confirmed. We propose as treatment for these selected cases an inversed Y cardioplasty + truncal vagotomy, a partial distal gastrectomy and Roux-en-Y gastrojejunostomy in order to facilitate esophageal emptying and avoid the appearance of postoperative gastroesophageal reflux as a side effect of this procedure. One patient was reoperated on in order to enlarge the cardioplasty. Disappearance of dysphagia was confirmed in all patients. Three patients presented reflux symptoms and were treated with 20 mg of Omeprazole 20 twice/day. No food retention, erosive esophagitis, or Barrett's esophagus were observed. The mean resting pressure decreased from 24.9 +/- 8.5 mm Hg to 7.5 +/- 2.5 mm Hg (P = 0.0001). Furthermore, esophageal diameter decreased significantly after a 5-year follow-up. This procedure could be an option for treating patients in which repeated Heller operations have failed.

PLAST RECONSTR SURG. 2010 AUG;126(2):375-84.

IS A SECOND FREE FLAP STILL AN OPTION IN A FAILED FREE FLAP BREAST RECONSTRUCTION?

Hamdi M, **Andrades P**, Thiessen F, Stillaert F, Roche N, Van Landuyt K, Monstrey S.

BACKGROUND: Salvage of a failed autologous breast reconstruction is a complex and challenging problem. The purpose of this study was to analyze the indications, methods, and outcomes of tertiary surgery in patients with a failed autologous breast reconstruction. METHODS: A retrospective chart review was performed for all patients who underwent breast reconstruction with autologous tissue performed by the senior author (M.H.) between 2002 and 2009. Special emphasis was made to evaluate the first reconstruction performed, causes of failure, indications for tertiary reconstruction, and outcomes. A preoperative hematologic workout was performed. For patients who were classified within the highest group of thromboembolism, specific prophylactic measurements were taken for the tertiary surgery. RESULTS: Of 688 patients who underwent autologous breast reconstruction, a total of 14 patients required tertiary breast reconstruction. Hypercoagulability was found in three patients resulting from disorders such as lupus anticoagulant positivity and antiphospholipid syndrome. Six patients (43 percent) underwent a combination of local skin flaps and/or implant reconstructions. Eight patients (57 percent) underwent nine microvascular breast reconstructions: five superior gluteal artery perforator flaps, three transverse myocutaneous gracilis flaps, and one deep inferior epigastric artery perforator flap. Two of nine flaps (22 percent) required quaternary reconstructions because of a failure of the second free flap. Additional corrections such as revision lipofilling, scar revision, contralateral breast shaping, implant change, and capsulotomies were performed in 92.7 percent of the patients, with a mean follow-up of 37 months (range, 6 months to 7 years). CONCLUSIONS: Tertiary surgery after autologous breast reconstruction failure has limited options and further reoperations are often needed. Careful patient history and

selective blood tests may reveal hidden coagulation disorders. When a second free flap is planned, primary and secondary antithrombotic therapy should be considered.

J GASTROINTEST SURG. 2010 NOV 9.

LAPAROSCOPIC RESECTIONAL GASTRIC BYPASS IN PATIENTS WITH MORBID OBESITY: EXPERIENCE ON 112 CONSECUTIVE PATIENTS.

Braghetto I, Csendes A, Korn O, Gutierrez L, Brunet L, Lanzarini E, Mushle M, Valladares H, Rojas J.

INTRODUCTION: Gastric bypass, without gastric resection of the distal excluded stomach, is the surgical treatment more frequently performed for morbid obesity. Several postoperative complications related to the "in situ" distal stomach have been described, and few cases of undetected gastric carcinoma located in this segment of stomach have been published. In this paper, we present our early postoperative results in patients submitted to laparoscopic gastric bypass with resection of distal stomach in patients with morbid obesity. METHODS: One hundred twelve consecutive patients were included in this study. The mean body weight was 112.15 ± 5.1 (range 78-145), and BMI was 40.5 ± 6.9 kg/m(2) (32.9-50.3). Patients were submitted to resectional gastric bypass by laparoscopic approach. The operative time was 133.7 ± 29.1 min (range 120-240). RESULTS: Postoperative complications occurred in 12 patients (10.7%) without any mortality. Early complications were observed in 11 patients while one patient presented a late complication, four patients were re-hospitalized, three of them without operation and other four of them were re-operated due to early (three patients) or late complication (one patient). One hundred patients (89.2%) were discharged at fourth postoperative day, seven patients remained in hospital between 5 and 10 days, and four patients after the tenth day due to complications. Leaks were observed in three patients. The histological study of the resected specimen was normal in only 8.9%. CONCLUSIONS: Laparoscopic resectional gastric bypass presents very similar results compared to classic gastric bypass, without significant increase of morbidity, mortality, early and late postoperative results, and therefore, it is an option for the surgical treatment of morbid obesity in countries with high risk of gastric carcinoma.

AESTHETIC PLAST SURG. 2010 OCT;34(5):547-9.

LEADERSHIP IN PLASTIC SURGERY TODAY.

Prado A, Parada F.

This article was developed after the authors heard young plastic surgeons of their unit ask what attribute makes people want to follow a leader. What people most seek to find in a leader has been constant over time and shared in different countries, genders, and age groups. These qualities include honesty, a forward-looking perspective, inspiration, and competence (Kouzes and Posner, Clin Lab Manage Rev 8:340, 1994). However, the residents and fellows thought differently and told the authors how "they" wanted to be seen when they became leaders. They wanted to viewed as shifting engines pulling forward teams of plastic surgery as hard as possible, leaving space for followers to develop and grow. They also wanted to be seen as having impeccable behavior related to the assumption of obligations, and finally as having the "most" informal authority possible, an authority that is not negotiable because it is given by peers to the leader due to personal qualities and actions. Obtaining formal authority at a very young age is fine, but if a surgeon's associates have not given him or her informal authority, the surgeon is only the "boss" and not the leader of the group. Informal authority is constructed over a time line and given by others to the leader because of what he or she has in values and personal attitudes and because of what the leader has done and can go on doing with sustained credibility and competency. Therefore, it is the authors' opinion that the exercise of leadership in plastic surgery is supported by informal authority and that the leader of leaders will be the one who has the most of this attribute that never is given formally.

J GASTROINTEST SURG. 2010 SEP;14(9):1343-8.

MANAGEMENT OF LEAKS AFTER LAPAROSCOPIC SLEEVE GASTRECTOMY IN PATIENTS WITH OBESITY.

Csendes A, Braghetto I, León P, **Burgos AM.**

INTRODUCTION: Laparoscopic sleeve gastrectomy (LSG) is a surgical procedure that is being increasingly performed on obese patients. The most frequent postoperative complication is the appearance of a gastric leak. PURPOSE: To determine the main clinical features of a group of patients who developed a gastric leak after LSG. MATERIAL: A total of 343 obese patients were submitted to LSG, two hundred and sixty-two women and 81 men with a mean age of 37.3 years and a BMI of 37.5 kg/m(2). Radiological evaluations were performed on all patients on the third day after surgery using liquid sulfate barium, as well as a close clinical control evaluation to monitor the appearance of epigastric pain,

fever, tachycardia, C-reactive protein, and leukocytosis. Medical or surgical management of the leak were employed. RESULTS: Fever was the earliest and most frequent symptom, followed by epigastric pain and tachycardia. Leaks were classified based on three parameters: severity or magnitude, location, and time of appearance after surgery. Leaks were classified as early if they appeared 1 to 4 days after surgery, intermediate if they appeared 5 to 9 days after surgery, and late 10 days after surgery. The diagnosis of a leak was confirmed with a barium liquid taken orally by six patients and with an abdominal CAT scan in ten. Surgical management was performed in eight patients, usually in those with early leaks (six patients). Early re-suturing in three patients was successful; however, re-suturing leaks after the third day resulted in failure. Medical management was performed mainly in patients with intermediate and late leaks, mainly through enteral nutrition and percutaneous drainage of the intra-abdominal fluid collection. There was no mortality. The mean healing days of these leaks was 45 days after surgery. CONCLUSION: Close clinical observation detects gastric leaks early on inpatients who underwent LSG. We suggest evaluating these leaks based on three parameters: time of appearance, the location, and its severity, in order to propose the best medical or surgical treatment in these patients.

OBES SURG. 2010 MAR;20(3):357-62.

MANOMETRIC CHANGES OF THE LOWER ESOPHAGEAL SPHINCTER AFTER SLEEVE GASTRECTOMY IN OBESE PATIENTS.

Braghetto I, Lanzarini E, Korn O, Valladares H, Molina JC, Henriquez A.

INTRODUCTION: Laparoscopic sleeve gastrectomy has been accepted as an option for surgical treatment of obesity. After surgery, some patients present reflux symptoms associated with endoscopic esophagitis, therefore PPI's treatment must be indicated. PURPOSE: This study aims to evaluate the manometric characteristic of the lower esophageal sphincter (LES) before and after sleeve gastrectomy MATERIAL AND METHOD: This prospective study includes 20 patients submitted to esophageal manometry in order to determine the resting pressure, and total and abdominal LES length before and after the sleeve gastrectomy. Statistical variations on the LESP were validated according to Student's "t" test. RESULTS: Seventeen female and three male patients were included, with a mean age of 37.6 +/- 12.6 years. All patients reduced their body weight, from an initial BMI of 38.3 kg/m(2) to 28.2 kg/m(2) 6 months after surgery. No postoperative complications were observed in these patients. Preoperative mean LESP was 14.2 +/- 5.8 mmHg. Postoperative manometry decreased in 17/20 (85%), with a mean value of 11.2 +/- 5.7 mmHg ($p = 0.01$). Seven of them presented LESP <12 mmHg and ten patients <6 mmHg after the operation. Furthermore, the abdominal length and total length of the high pressure zone at the esophagogastric junction were affected. CONCLUSION: A sleeve gastrectomy produces an important decrease in LES pressure, which can in turn cause the appearance of reflux symptoms and esophagitis after the operation due to a partial resection of the sling fibers during the gastrectomy.

INT SURG. 2010 JAN-MAR;95(1):80-7.

POSTOPERATIVE RESULTS AFTER LAPAROSCOPIC APPROACH FOR TREATMENT OF LARGE HIATAL HERNIAS: IS MESH ALWAYS NEEDED? IS THE ADDITION OF AN ANTIREFLUX PROCEDURE NECESSARY?

Braghetto I, Korn O, Csendes A, Burdiles P, Valladares H, Brunet L.

Laparoscopic approach has been suggested as the definitive treatment for large hiatal hernias. Reinforcement of the hiatoplasty and the need to perform antireflux surgery is still undergoing discussion. The purpose of this study was to evaluate the postoperative results, with special emphasis on the recurrence rate and reflux after surgery comparing the use or not of mesh reinforcement. This prospective study included 81 patients with a complete evaluation through a clinical questionnaire, barium sulfate radiologic evaluation, endoscopy, manometry, and 24-hour intraesophageal pH monitoring before and after a hiatoplasty with an antireflux procedure. Mesh reinforcement was used in 23 patients. Postoperative complications occurred in 11 patients (13.6%), without mortality. Recurrent hernia was observed in 10 patients without mesh reinforcement (12.3%), whereas those with mesh reinforcement showed no hiatal hernia recurrence ($P = 0.33$). Normal resting lower esophageal sphincter pressure was obtained after fundoplication in 87.2% of patients, and abnormal acid reflux was observed in 12.8% of patients after surgery. In conclusion, mesh reinforcement in patients with large Type IV could prevent recurrent hiatal hernias, and an antireflux procedure must be performed in order to avoid postoperative acid reflux.

J PLAST RECONSTR AESTHET SURG. 2010 OCT;63(10):1581-7.

RECENT DEVELOPMENTS IN THE ABILITY TO PREDICT AND MODIFY BREAST CANCER RISK.

Prado A, **Andrades P**, Parada F.

The identification of women at higher risk for breast cancer is a matter of public health and anyone who participates in any treatment modality of this condition (this includes the plastic surgeon) should be aware of the tools and predictive models of breast cancer. Screening for breast cancer in the community, and probably during the daily plastic surgery consultation, until recently, was limited to decisions about when to initiate a mammography study. New developments that predict and modify breast cancer risk must be clearly understood by our specialty through identification of women at higher risk for breast cancer and be familiar with the current issues related to screening and risk-reduction measures. In this review, we discuss current knowledge regarding the recent data of breast cancer risk, screening strategies for high-risk women and medical and surgical approaches to reduce breast cancer risk. Patients with breast cancer belong to one of three groups: a. Sporadic breast cancer (75%)--patients without family history or those who have a breast biopsy with proliferative changes. b. Genetic mutation breast cancer (5%)--women who have a genetic predisposition, and most of these are attributable to mutations in the breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2). c. Cluster family breast cancer (20%)--seen in women with a relevant history of breast cancer in the family and breast biopsy with proliferative breast changes with no association with mutations.Those at high risk for breast cancer should investigate the family history with genetic testing consideration, clinical history, including prior breast biopsies and evaluation of mammographic density. Tools for breast cancer risk assessment include the Gail and Claus model, genetic screening,BRCAPRO and others that are evaluated in this review.

TOXICON. 2010 JAN;55(1):135-44.

ROUTE OF METABOLIZATION AND DETOXICATION OF PARALYTIC SHELLFISH TOXINS IN HUMANS.

García C, Barriga A, **Díaz JC,** Lagos M, Lagos N.

Paralytic shellfish toxins (PST) are a collection of over 26 structurally related imidazoline guanidinium derivatives produced by marine dinoflagellates and freshwater cyanobacteria. Glucuronidation of drugs by UDP-glucuronosyltransferase (UGT) is the major phase II conjugation reaction in mammalian liver. In this study, using human liver microsomes, the in vitro paralytic shellfish toxins oxidation and sequential glucuronidation are achieved. Neosaxitoxin (neoSTX), Gonyautoxin 3/2 epimers (GTX3/GTX2) and Saxitoxin (STX) are used as starting enzymatic substrates. The enzymatic reaction final product metabolites are identified by using HPLC-FLD and HPLC/ESI-IT/MS. Four metabolites from GTX3/GTX2 epimers precursors, three of neoSTX and two of STX are clearly identified after incubating with UDPGA/NADPH and fresh liver microsomes. The glucuronic-Paralytic Shellfish Toxins were completely hydrolysed by treatment with beta-glucuronidase. All toxin analogs were identified comparing their HPLC retention time with those of analytical standard reference samples and further confirmed by HPLC/ESI-IT/MS. Paralytic Shellfish Toxins (PST) were widely metabolized by human microsomes and less than 15% of the original PST, incubated as substrate, stayed behind at the end of the incubation. The apparent V(max) and Km formation values for the respective glucuronides of neoSTX, GTX3/GTX2 epimers and STX were determined. The V(max) formation values for Glucuronic-GTX3 and Glucuronic-GTX2 were lower than Glucuronic-neoSTX and Glucuronic-STX (6.8+/-1.9x10(-3); 8.3+/-2.8x10(-3) and 9.7+/-2.8x10(-3)pmol/min/mg protein respectively). Km of the glucuronidation reaction for GTX3/GTX2 epimers was less than that of glucuronidation of neoSTX and STX (20.2+/-0.12; 27.06+/-0.23 and 32.02+/-0.64microM respectively). In conclusion, these data show for the first time, direct evidence for the sequential oxidation and glucuronidation of PST in vitro, both being the initial detoxication reactions for the excretion of these toxins in humans. The PST oxidation and glucuronidation pathway showed here, is the hepatic conversion of its properly glucuronic-PST synthesized, and the sequential route of PST detoxication in human.

J PLAST RECONSTR AESTHET SURG. 2011 MAR;64(3):353-9.

SALVAGE (TERTIARY) BREAST RECONSTRUCTION AFTER IMPLANT FAILURE.

Hamdi M, Casaer B, **Andrades P**, Thiessen F, Dancey A, D'Arpa S, Van Landuyt K.

BACKGROUND: Salvage breast reconstruction is defined as a complete revision of a previous reconstruction in case of unsatisfactory results or failure of primary or secondary breast reconstruction. We have termed this 'tertiary breast reconstruction'. This article presents our experience with tertiary reconstructions, including the indications, method of reconstruction and outcomes. METHODS: A retrospective note review was performed for all patients who underwent breast reconstruction with autologous tissue under one surgeon between 2002 and 2009 at the University Hospital,

Ghent. Out of these 688 patients, 54 patients (7.8%) required tertiary surgery with autologous tissue after failure of implant breast reconstruction. RESULTS: The first reconstructive surgery involved 38 unilateral and 16 bilateral cases with a total of 70 operated breasts. A further 11 breasts were reconstructed following risk-reducing mastectomy or at the patient's request for aesthetic reasons. Out of 81 free-flap reconstructions, the deep inferior epigastric artery perforator (DIEAP) flap was the most harvested at 66 (81%). The mean±SD operating time was 7.2±1.8h and the mean hospital stay was 7.2±1.9 days. One total flap loss (1.2%) occurred. The mean follow-up was 31 months with a range between 3 months and 6 years. During follow-up, 30 patients (55.5%) needed secondary procedures to improve the aesthetic outcome. Donor-site corrections were performed in 18 patients (33%). Revisions of the breast flap were performed in 29 patients (53%). CONCLUSIONS: Restoring the breast envelope and footprint, in addition to excision of scar tissue, is the key step in breast reconstruction. Further corrections are required depending on the amount of the initial damage to the breast or subsequent postoperative complications.

OBES SURG. 2009 NOV;19(11):1515-21.

SCINTIGRAPHIC EVALUATION OF GASTRIC EMPTYING IN OBESE PATIENTS SUBMITTED TO SLEEVE GASTRECTOMY COMPARED TO NORMAL SUBJECTS.

Braghetto I, Davanzo C, Korn O, Csendes A, Valladares H, Herrera E, Gonzalez P, Papapietro K.

BACKGROUND: Sleeve gastrectomy (SG) has been accepted as an option for surgical treatment for obesity. This operation could be associated with motor gastric dysfunction and abnormal gastric emptying. The purpose of this prospective study is to present the results of gastric emptying to liquids and solids using scintigraphy in patients who underwent SG compared to normal subjects. METHODS: Twenty obese patients were submitted to laparoscopic SG and were compared to 18 normal subjects. Gastric emptying of liquids and solids was measured by scintigraphic technique. Results were expressed as half time of gastric emptying and the percentage of retention at 20, 30, and 60 min for liquids and at 60, 90, and 120 min for solids. RESULTS: In the group of operated patients, 70% of them (n = 14) presented accelerated emptying for liquids and 75% (n = 15) for solids compared to 22.2% and 27.7%, respectively, in the control group. The half time of gastric emptying (T (1/2)) in patients submitted to SG both for liquids and solids were significantly more accelerated compared to the control group (34.9 +/- 24.6 vs 13.6 +/- 11.9 min for liquids and 78 +/- 15.01 vs 38.3 +/- 18.77 min for solids; $p < 0.01$). The gastric emptying for liquids expressed as the percentage of retention at 20, 30, and 60 min was 30.0 +/- 0.25%, 15.4 +/- 0.18%, and 5.7 +/- 0.10%, respectively, in operated patients, significantly less than the control subjects ($p < 0.001$). For solids, the percentage of retention at 60, 90, and 120 min was 56 +/- 28%, 34 +/- 22%, and 12 +/- 8%, respectively, for controls, while it was 25.3 +/- 0.20%, 9 +/- 0.12%, and 3 +/- 0.05%, respectively, in operated patients ($p < 001$). CONCLUSIONS: Gastric emptying after SG is accelerated either for liquids as well as for solids in the majority of patients. These results could be taken in consideration for the dietary indications after surgery and could play a significant role in the definitive results during the late follow-up.

DEPARTAMENTO DE DERMATOLOGÍA

J ULTRASOUND MED. 2010 MAY;29(5):803-16.

BENIGN TUMORS AND PSEUDOTUMORS OF THE NAIL: A NOVEL APPLICATION OF SONOGRAPHY.

Wortsman X, Wortsman J, Soto R, **Saavedra T, Honeyman J, Sazunic I**, Corredoira Y.

OBJECTIVE: The purpose of this study was to determine the scope of high-resolution sonography in the detection of benign tumors and pseudotumors of the nail unit. METHODS: We performed a retrospective study of the sonographic findings in 103 consecutive patients with benign tumors and pseudotumors of the nail that were medically derived and confirmed histologically. Statistical analysis (Student t test) was performed comparing clinical and sonographic diagnoses. RESULTS: Common benign tumors and pseudotumors of the nail can be detected on sonography, and they present different sonographic morphologic characteristics. According to origin, the lesions were considered ungual in 73% (n = 75) and periungual in 27% (n = 28) of the cases. Sonography showed their nature (solid or cystic), location, and extension as well as regional blood flow. In 35% of the cases, the use of sonography modified the clinical diagnosis, although the detailed anatomic information provided by sonography was useful in the planning of surgery in all cases. The addition of sonography was significant ($P < .001$) for the diagnosis of subungual exostosis and granulomas in comparison to clinical diagnosis. CONCLUSIONS: Sonography is a noninvasive imaging method that can reliably detect common benign tumors and pseudotumors of the nail and provide precise data about their characteristics. This imaging modality can support diagnosis and surgery and can allow a better definition and improvement of the cosmetic outcome of the treatment.

DEPARTAMENTO DE MEDICINA

GASTROENTEROLOGÍA

OBESITY (SILVER SPRING). 2010 JUL;18(7):1460-3.

DECREASED LIVER FATTY ACID DELTA-6 AND DELTA-5 DESATURASE ACTIVITY IN OBESE PATIENTS.

Araya J, Rodrigo R, Pettinelli P, **Araya AV**, **Poniachik J**, Videla LA.

Steatosis in obese nonalcoholic fatty liver disease (NAFLD) patients is a clinicopathological condition associated with depletion of n-3 polyunsaturated fatty acids (PUFA), a feature that may be related to PUFA desaturation. Liver Delta-6 and Delta-5 desaturase (Delta-6D and Delta-5D) activities, homeostasis model assessment of insulin resistance (HOMA(IR)), and ferric reducing ability of plasma (FRAP) were evaluated in 13 obese patients who underwent subtotal gastrectomy with gastro-jejunal anastomosis in Roux-en-Y and 15 nonobese patients who underwent laparoscopic cholecystectomy (controls). Liver Delta-6D and Delta-5D activities in obese patients were 87% and 66% lower than controls ($P < 0.001$), respectively, with a 62% diminution in the Delta-6D/Delta-5D activity ratio ($P < 0.02$). Delta-6D inversely correlated with both HOMA(IR) ($r = -0.70$, $P < 0.0001$) and oxidative stress assessed as the reciprocal value of FRAP ($r = -0.40$, $P < 0.05$). Delta-5D negatively correlated with HOMA(IR) ($r = -0.48$, $P < 0.01$) but not with FRAP(-1) ($r = -0.13$, not significant). In conclusion, liver PUFA desaturation is diminished in obese NAFLD patients, in association with underlying insulin resistance and oxidative stress, which may play a role in altering lipid metabolism favoring fatty infiltration.

DIG DIS SCI. 2011 JAN;56(1):155-60.

SMALL INTESTINAL CLUSTERED CONTRACTIONS AND BACTERIAL OVERGROWTH: A FREQUENT FINDING IN OBESE PATIENTS.

Madrid AM, Poniachik J, Quera R, Defilippi C.

BACKGROUND: Small intestinal bacterial overgrowth (SIBO) has been observed in several disorders of the gastrointestinal tract. Studies have shown abnormalities of motor function in obese patients, and there is indirect evidence suggesting that SIBO is present in them. AIMS: To study small intestinal motility and the prevalence of SIBO in obese patients and to determine whether there was any relationship between both parameters. METHODS: Thirty-nine patients scheduled for bariatric surgery were subjected to hydrogen breath test with lactulose and to a stationary small intestinal motility study with perfused catheters. RESULTS: SIBO was observed in 41% of obese patients and was not related to body mass index. Small intestinal manometry showed a marked increase of clustered contractions in obese patients with SIBO compared to obese subjects without SIBO, whereas all the other parameters of fasting cyclic activity were not different. CONCLUSIONS: SIBO was a frequent finding in obese patients and was associated with an increased pattern of clustered contractions, which was not observed in absence of SIBO.

INMUNOLOGÍA

TRANSPLANT PROC. 2010 JAN-FEB;42(1):266-9.

EVALUATION OF HLA MATCHMAKER COMPATIBILITY AS PREDICTOR OF GRAFT SURVIVAL AND PRESENCE OF ANTI-HLA ANTIBODIES.

Silva E, Alba A, Castro A, Carrascal M, Buckel E, Aguiló J, Herzog C, Calabrán L, Morales J, Fierro JA.

BACKGROUND: HLA Matchmaker is a computer algorithm developed to evaluate donor/receptor compatibility comparing sequences of polymorphic aminoacids (eplets) present in human leukocyte antigen (HLA) molecules. The aim of this study was to evaluate the predictive value of HLA Matchmaker for patient and graft survival, graft survival free of rejection, and the presence of anti HLA antibodies. METHODS: Using this program, 62 of 173 kidney transplant patients, were retrospectively analyzed. HLA-I loci eplet mismatch value (EMM) was determined and correlated with graft survival, graft survival free of rejection, and the presence of anti HLA-I antibodies. EMM was compared with the traditional HLA antigen mismatch value (MM) in terms of the presence of anti HLA-I antibodies. RESULTS: Graft survival and graft survival free of rejection showed no statistical differences (P-value .975 and .365, respectively) while comparing patients with less or more than 10 HLA-I EMM. Patients with > or =6 HLA-B EMM had an odds ratio (OR) of 5.6 (95% confidence interval [CI], 0.47-66.45) of presenting anti HLA-I antibodies, with a sensitivity of 80% and specificity of 58.3%. For > or =2 HLA-B MM, the OR was 2.58 (95% CI, 0.46-14.5), with a sensitivity of 40% and specificity of 75%. CONCLUSION: Even though in our study population compatibility by HLA Matchmaker did not correlate with graft survival or rejection-free graft survival, it showed a better sensitivity than traditional HLA antigen matching for the presence of anti HLA-I antibodies. HLA Matchmaker is a promising tool in predicting the appearance of anti-HLA antibodies.

MEDICINA NUCLEAR

CLIN NUCL MED. 2010 NOV;35(11):862-4.

A COMPARISON BETWEEN TWO IMAGING TECHNIQUES FOR THE DIAGNOSIS OF SUBACUTE THYROIDITIS (DE QUERVAIN THYROIDITIS): BRIEF COMMUNICATION.

González P, Guendelman CL, Quevedo Limón LN, Fernández RJ.

PURPOSE: Subacute thyroiditis (SAT) or de Quervain thyroiditis is a relatively frequent and self-limited condition with a triphasic clinical course. Its symptoms can mimic other thyroid, upper respiratory, and ear infections. Thyroid ultrasonography (TUS), radioactive iodine uptake (RAIU), and thyroid scintigraphy (TS) may be used for differential diagnosis. To assess and compare the diagnostic value of thyroid TUS and TS in patients on the first phase of a clinically diagnosed SAT. MATERIAL AND METHODS: Twenty-two patients (18 women and 4 men, age, 37.2 ± 9.83 years) with clinical diagnosis of SAT were prospectively studied. Thyroid stimulating hormone, T3, free T4, antithyroperoxidase antibodies, thyroglobulin, polymerase chain reaction, complete blood count and differential, TUS, TS, and RAIU at 2 and 24 hours were performed. RESULTS: All patients were on thyrotoxic phase with a thyroid stimulating hormone mean of 0.03 ± 0.030 mU/L (range: 0.005-0.13); antithyroperoxidase antibodies were positive in 3 patients (≥75 UI/mL); thyroglobulin was elevated in 16 patients (≥55 ng/mL). RAIU at 2 hours was 1.94% ± 0.85% (range: 1%-4%), and at 24 hours, 0.98% ± 1.24% (range: 0.10%-5%). TS showed low uptake in all patients. On TUS, only 8 patients were compatible with SAT. In 13 patients, TUS was consistent with goiter, diffuse type in 8, multinodular in 5, and normal in 1 patient. CONCLUSION: Low thyroid scan uptake with I-131 at 2 hours (<4%) and 24 hours (<5%), and poor thyroid visualization on TS seem to be more prevalent than focal distortion and heterogeneity in TUS in thyrotoxic phase of SAT.

REV ESP MED NUCL. 2010 NOV-DEC;29(6):293-8.

INFLUENCE OF EXTRACARDIAC ACTIVITY AND PERFUSION ABNORMALITIES ON MYOCARDIAL PERFUSION GATED SPECT PARAMETERS: INTEROBSERVER ANALYSIS.

Jaimovich R, Gutiérrez D, Lavados H, Aqueveque C, Quevedo L, **Alay R, Massardo T.**

OBJECTIVE: Extracardiac activity (ECA) may affect interpretation of gated SPECT myocardial perfusion studies (MPSs). To solve this problem, available softwares include myocardial edge delimitation. PURPOSE: To evaluate the influence of ECA in automatic myocardial edge detection under normal conditions and with abnormal perfusion and also evaluate the reproducibility of semi-automatic processing. METHODS: A total of 100 MPSs, 50 with ECA, were analyzed. Each subgroup included 25 cases with perfusion abnormalities. The cases were processed automatically and by 4 independent operators with different levels of experience. Commercial QGS and QPS softwares were used with tools to mask and relocate the left ventricle area. Functional parameters (final diastolic and systolic volumes and ejection fraction) and perfusion parameters such as the reversibility perfusion score and rest perfusion defect extension were analyzed. The data were compared with Pearson's correlation and Student's test. RESULTS: Interobserver correlation significantly worsened with the presence of ECA and was moderately affected by perfusion abnormalities. More experienced observers presented better correlation. Reproducibility was greater for the functional perfusion parameters, independently of the observer's experience. CONCLUSIONS: ECA significantly affects automatic edging delimitation, affecting the MPS values. Interobserver reproducibility with manual processing was more altered regarding functional parameters than in the perfusion scores. Perfusion abnormalities did not interfere with software reproducibility, and when present, better correlation was found. If ECA is not present, manual intervention should be avoided.

EUR J NUCL MED MOL IMAGING. 2010 APR;37(4):758-64.

MOTION CORRECTION AND MYOCARDIAL PERFUSION SPECT USING MANUFACTURER PROVIDED SOFTWARE. DOES IT AFFECT IMAGE INTERPRETATION?

Massardo T, Jaimovich R, Faure R, Muñoz M, **Alay R, Gatica H.**

PURPOSE: Myocardial perfusion SPECT is an excellent tool for the assessment of coronary artery disease (CAD); however, it is affected by several artifacts, such as patient motion during acquisition, which increases false-positive rates. Therefore, the purpose of this work is to analyze changes in perfusion scores after motion-correction software application. METHODS: The population included 160 (99m)Tc-sestamibi CAD studies, divided into two groups: with and without perfusion defects, equally divided into subgroups according to movement during standard acquisition. A Siemens ECAM 180 was used for processing without correction and with automatic and manual e.soft 2.5 modalities. Visual interpretation as well as QPS software was compared using Pearson correlation and kappa agreement statistics. RESULTS: Moderate agreement was observed between SPECT interpretations after motion correction versus the original report, according to the presence of perfusion defects.

Manual correction using the software obtained the lowest agreements. Perfusion summed stress scores (SSS) correlation from different processing modalities versus non-corrected studies differed significantly independent of the degree of motion. Mean SSS in 40 patients with no motion was 3.9 + or - 3.9 when no correction was applied; with automatic correction was 8.8 + or - 10 (p = 0.03) and with manual correction was 3.1 + or - 3.5 (p = ns versus non-corrected). Automatic correction was better when applied to patients with mild to moderate motion. In those with mild or no motion, software overestimated or created new perfusion defects. CONCLUSION: Motion-correction software must be used with caution when trying to optimize myocardial perfusion SPECT based on individual analysis. Acquisition should be always repeated in cases with severe motion and in no or mild motion it seems preferable to avoid correction.

NEFROLOGÍA

NUTR HOSP. 2010 JUL-AUG;25(4):682-7.

[BODY COMPOSITION ASSESSMENT IN PATIENTS WITH CHRONIC RENAL FAILURE].

Cano M, Camousseigt J, Carrasco F, Rojas P, Inostroza J, Pardo A, Faundez V, Loncon P, **Pacheco A, Sanhueza ME.**

INTRODUCTION: Assessment of body composition is paramount in early assessment of nutritional status impairments due to excess or deficit. There are, however, few field reliable methods for this objective for patients with chronic renal failure (CRF.). OBJECTIVE: To assess the reliability of the estimations of body composition by different methods as compared to dual energy X-ray absorptiometry (DEXA) as the gold standard method in patients with CRF and on regular chronic haemodialysis. PATIENTS AND METHODS: We assessed body composition in 30 haemodialysis patients (46.9 +/- 15.1 years (18-76); BMI 25.9 +/- 5.7 kg/m(2) (18.1-41.5)), observing agreement in the percentage of fat mass (%FM) between the sum of the 4 folds (SP; calibrator Lange) and bioimpedantiometry by using different equations (BIA; Biodynamics 450) versus DEXA (Lunar DPX-L). RESULTS: (X +/- SD) By BMI, 3 subjects had low weight (10%), 14 normal weight (46.7%), 7 overweight (23.3%), and 6 obesity (20%). The %FM with SP (30.7 +/- 7.1%) significantly differed from DEXA (27.3 +/- 10.3%; $p < 0.001$). With BIA there was a significant difference in %FM with the Deurenberg and Formica equations. The %FM obtained with the manufacturer's equations (Segal, Lukaski and Kyle) did not show a significant difference from DEXA. With Kyle's equation we observed a better agreement (difference with DEXA: -0.58 +/- 4.2%). CONCLUSIONS: We found a low percentage of patients with low weight as compared to previous studies. The skin folds show low reliability to estimate the fat mass. The bioimpedantiometry, using Kile's equation may be a good filed method to assess haemodialysis patients.

REUMATOLOGÍA

J NEUROIMMUNOL. 2010 OCT 8;227(1-2):153-61.

ANTIBODIES AGAINST THE VOLTAGE-DEPENDENT ANION CHANNEL (VDAC) AND ITS PROTECTIVE LIGAND HEXOKINASE-I IN CHILDREN WITH AUTISM.

Gonzalez-Gronow M, **Cuchacovich M,** Francos R, Cuchacovich S, Fernandez Mdel P, Blanco A, Bowers EV, Kaczowka S, Pizzo SV.

Autistic children show elevated serum levels of autoantibodies to several proteins essential for the function of normal brains. The voltage-dependent anion channel (VDAC) and hexokinase-I, a VDAC protective ligand, were identified as targets of this autoimmunity in autistic children. These autoantibodies were purified using immunoaffinity chromatographic techniques. Both antibodies induce apoptosis of cultured human neuroblastoma cells. Because VDAC and hexokinase-I are essential for brain protection from ischemic damage, the presence of these autoantibodies suggests a possible causal role in the neurologic pathogenesis of autism.

ARTHRITIS RES THER. 2010;12(2):R68.

B CELLS FROM RHEUMATOID ARTHRITIS PATIENTS SHOW IMPORTANT ALTERATIONS IN THE EXPRESSION OF CD86 AND FCGAMMARIIB, WHICH ARE MODULATED BY ANTI-TUMOR NECROSIS FACTOR THERAPY.

Catalán D, Aravena O, **Sabugo F**, **Wurmann P, Soto L**, Kalergis AM, **Cuchacovich M**, Aguillón JC; Millenium Nucleus on Immunology and Immunotherapy P-07-088-F.

INTRODUCTION: Several molecules help preserve peripheral B cell tolerance, but when altered, they may predispose to autoimmunity. This work studied the expression of the costimulatory molecule CD86 and the inhibitory receptor for IgG immune complexes FcgammaRIIb (CD32b), on B cells from rheumatoid arthritis (RA) patients, and the influence of anti-tumor necrosis factor (TNF) therapy. METHODS: Peripheral B cells from 18 RA patients and 13 healthy donors were characterized using flow cytometry. Eleven patients who underwent a six-month adalimumab therapy were further

assessed for phenotypic changes on their B cells. RESULTS: RA patients exhibited a high percentage of naïve and memory B cells expressing CD86. In contrast, expression of FcgammaRIIb was significantly reduced on RA memory B cells and plasmablasts as compared to healthy donors, probably due to downregulation of this receptor when differentiating from naïve to memory cells. These alterations on FcgammaRIIb were associated with high levels of anti-citrullinated vimentin autoantibodies. In addition, treatment with adalimumab normalized the expression of CD86 on memory B cells and reduced the expression of FcgammaRIIb, mainly on naïve B cells. CONCLUSIONS: Our findings show that peripheral B cells from RA patients have an altered expression of key molecules, such as CD86 and FcgammaRIIb. Because this latter receptor is required for feedback inhibition, a deficient expression might contribute to humoral autoimmune responses. Furthermore, these molecules are likely to be influenced by inflammatory factors, since they were modulated by TNF inhibition.

OCUL IMMUNOL INFLAMM. 2010 JUN;18(3):200-7.

COMPARISON OF THE CLINICAL EFFICACY OF TWO DIFFERENT IMMUNOSUPPRESSIVE REGIMENS IN PATIENTS WITH CHRONIC VOGT-KOYANAGI-HARADA DISEASE.

Cuchacovich M, Solanes F, Díaz G, Cermenati T, Avila S, Verdaguer J, Verdaguer JI, Carpentier C, Stopel J, Rojas B, Traipe L, Gallardo P, **Sabugo F**, Zanoli M, Merino G, Villarroel F.

PURPOSE: To prospectively compare 2 immunosupressive regimens in patients with active Vogt-Koyanagi-Harada disease in spite of systemic glucocorticoid treatment. METHODS: Forty-four patients were diagnosed between 1998 and 2005. Twenty-one developed chronic intraocular inflammation in spite of glucocorticoid treatment and were randomized to receive either prednisone and azathioprine (AZA) (n = 12) or prednisone and cyclosporine (CyA) (n = 9). RESULTS: In the AZA group Tyndall score decreased from 1.21 +/- 1.10 to 0.29 +/- 0.62 ($p < .01$), and visual acuity (LogMAR) improved from 0.32 +/- 0.35 to 0.09 +/- 0.16 ($p < .001$). In the CyA group Tyndall score decreased from 1.67 +/- 1.08 to 0.16 +/- 0.51 ($p < .001$), and visual acuity improved from 0.41 +/- 0.40 to 0.25 +/- 0.42 ($p < .001$). Patients in the AZA group needed a significantly higher average prednisone dose and total cumulative dose than those in the CyA group, $p < .01$ for each comparison. CONCLUSIONS: Both regimens showed a good clinical efficacy, but CyA seems to be a better glucocorticoid-sparing agent than AZA.

DEPARTAMENTO DE NEUROLOGÍA Y NEUROCIRUGÍA

NEUROLOGY. 2010 JAN 12;74(2):106-12.

CANCER LINKED TO ALZHEIMER DISEASE BUT NOT VASCULAR DEMENTIA.

Roe CM, Fitzpatrick AL, Xiong C, Sieh W, Kuller L, Miller JP, Williams MM, Kopan R, **Behrens MI**, Morris JC.

OBJECTIVE: To investigate whether cancer is associated with Alzheimer disease (AD) and vascular dementia (VaD). METHODS: Cox proportional hazards models were used to test associations between prevalent dementia and risk of future cancer hospitalization, and associations between prevalent cancer and risk of subsequent dementia. Participants in the Cardiovascular Health Study-Cognition Substudy, a prospective cohort study, aged 65 years or older (n = 3,020) were followed a mean of 5.4 years for dementia and 8.3 years for cancer. RESULTS: The presence of any AD (pure AD + mixed AD/VaD; hazard ratio [HR] = 0.41, 95% confidence interval [CI] = 0.20-0.84) and pure AD (HR = 0.31, 95% CI = 0.12-0.86) was associated with a reduced risk of future cancer hospitalization, adjusted for demographic factors, smoking, obesity, and physical activity. No significant associations were found between dementia at baseline and rate of cancer hospitalizations for participants with diagnoses of VaD. Prevalent cancer was associated with reduced risk of any AD (HR = 0.72; 95% CI = 0.52-0.997) and pure AD (HR = 0.57; 95% CI = 0.36-0.90) among white subjects after adjustment for demographics, number of APOE epsilon4 alleles, hypertension, diabetes, and coronary heart disease; the opposite association was found among minorities, but the sample size was too small to provide stable estimates. No significant association was found between cancer and subsequent development of VaD. CONCLUSIONS: In white older adults, prevalent Alzheimer disease (AD) was longitudinally associated with a reduced risk of cancer, and a history of cancer was associated with a reduced risk of AD. Together with other work showing associations between cancer and Parkinson disease, these findings suggest the possibility that cancer is linked to neurodegeneration.

J ALZHEIMERS DIS. 2010;21(3):757-61.

CLINICAL AND GENETIC ANALYSIS OF A CHILEAN FAMILY WITH EARLY-ONSET AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE.

Sinning M, van Rooyen JP, **Venegas-Francke P**, Vásquez C, **Behrens MI**, Ramírez A.

Autosomal dominant early-onset Alzheimer's disease (ADEOAD) is associated predominantly with mutations in the genes that codify for presenilin 1 (PSEN1). Only a few ADEOAD families have been reported from Latin America. This is an extended Chilean pedigree affected by ADEOAD along 4 generations. The age of onset of dementia was between 38 and 42 years. Early manifestations were anxiety and depression. Mutation analysis revealed a heterozygous G to C transversion at position 438 of the mRNA in PSEN1 in all affected members. This is the first report of a Chilean family with ADEOAD to include mutation analysis.

MOV DISORD. 2010 SEP 15;25(12):1929-37.

CLINICAL SPECTRUM OF KUFOR-RAKEB SYNDROME IN THE CHILEAN KINDRED WITH ATP13A2 MUTATIONS.

Behrens MI, Brüggemann N, Chana P, **Venegas P**, Kägi M, Parrao T, Orellana P, Garrido C, Rojas CV, Hauke J, Hahnen E, González R, Seleme N, Fernández V, Schmidt A, Binkofski F, Kömpf D, Kubisch C, Hagenah J, Klein C, Ramirez A.

We report the clinical features of the original Chilean family with Kufor-Rakeb syndrome (KRS) that led to the discovery of the ATP13A2 gene at the PARK9 locus. KRS is a rare juvenile-onset autosomal recessive disease characterized by progressive Parkinsonism, pyramidal signs, and cognitive decline in addition to vertical gaze palsy and facial-faucial-finger minimyoclonus. Neurological and neuropsychological examination during a 10-year period, videotaping, neuroimaging, and measurement of DNA methylation of the ATP13A2 promoter region were performed. The youngest 5 of 17 children of nonconsanguineous parents, carrying compound-heterozygous ATP13A2 mutations, had normal development until ages ~10 to 12 years, when school performance deteriorated and slowness, rigidity, and frequent falls developed. Examination revealed bradykinesia, subtle postural/action tremor, cogwheel rigidity, spasticity, upward gaze palsy, smooth pursuit with saccadic intrusions, and dementia. Additional signs included facial-faucial-finger minimyoclonus, absent postural reflexes, visual/auditory hallucinations, and insomnia. Levodopa response could not be fully judged in this family. T2* magnetic resonance imaging sequences revealed marked diffuse hypointensity of the caudate (head and body) and lenticular nucleus bilaterally. Disease progression was slow including epilepsy, cachexia, and anarthria. Four affected members died after 28.5 ± 5.5 (mean ± SD) years of disease. Two heterozygous carriers, the mother and eldest sibling, showed jerky perioral muscle contractions and clumsiness of hand movements. There was no significant correlation between DNA methylation of the ATP13A2 promoter region and disease progression. The marked caudate and lenticular nucleus T2*-hypointensity suggests that KRS might belong to the family of neurodegenerative diseases associated with brain iron accumulation.

STROKE. 2011 JAN;42(1):191-5.

COMPARATIVE EFFECTIVENESS OF HEMOSTATIC THERAPY IN EXPERIMENTAL WARFARIN-ASSOCIATED INTRACEREBRAL HEMORRHAGE.

Illanes S, Zhou W, Schwarting S, Heiland S, Veltkamp R.

BACKGROUND AND PURPOSE: intracerebral hemorrhage associated with oral anticoagulants has a poor prognosis. Current treatment guidelines are based on case series and plausibility only, and a common consensus on effective hemostatic therapy is missing. We compared the effectiveness of diverse hemostatic approaches in a mouse model of warfarin-associated intracerebral hemorrhage. METHODS: male C57BL/6 mice received anticoagulant treatment with warfarin (0.4 mg/kg for 3 days). Intracerebral hemorrhage was induced by striatal injection of collagenase, and 30 minutes later, mice received an intravenous injection of saline (200 μL n=15), prothrombin complex concentrate (100 U/kg, n=10), fresh-frozen plasma (200 μL, n=13), recombinant human Factor VII activated (3.5 mg/kg, n=8 and 10 mg/kg, n=8), or tranhexamic acid (400 mg/kg, n=12). Intracerebral hemorrhage volume was quantified on T2-weighted images after 24 hours. RESULTS: mean hematoma volumes were 7.4 ± 1.8 mm(3) in the nonwarfarin controls and 21.9 ± 5.0 mm(3) in the warfarin group receiving saline. Prothrombin complex concentrate (7.5 ± 2.3 mm(3)) and fresh-frozen plasma (8.7 ± 2.1) treatment resulted in significantly smaller hematoma volume compared with saline. Recombinant human Factor VII activated (10 mg/kg: 14.7 ± 3.4; 3.5 mg/kg: 15.0 ± 6.8 mm(3)) and tranexamic acid (16.2 ± 4.1 mm(3)) were less effective. Water content in the hemorrhagic hemisphere was similar in all groups except for tranexamic acid in which it was significantly increased. CONCLUSIONS:

prothrombin complex concentrate and fresh-frozen plasma effectively prevent hematoma growth in murine warfarin-associated intracerebral hemorrhage, whereas Factor VIIa was less effective. Tranexamic acid exacerbates perihematoma edema in this mouse warfarin-associated intracerebral hemorrhage model.

DEMENT GERIATR COGN DISORD. 2010;29(5):397-405.

FREQUENCY AND DETERMINANTS OF POSTSTROKE COGNITIVE IMPAIRMENT AT THREE AND TWELVE MONTHS IN CHILE.

Delgado C, Donoso A, Orellana P, Vásquez C, **Díaz V, Behrens MI.**

BACKGROUND: A higher risk of poststroke cognitive impairment (CI) has been reported in Hispanics in a US cohort but has not been systematically studied in Latin America. OBJECTIVES: Our purpose was to investigate the frequencies and determinants of poststroke CI in the hispano-mestizo population of Santiago, Chile.
METHODS: A prospective study of hospitalized patients aged >60 years admitted with an ischemic or hemorrhagic stroke was conducted. The cognitive status was determined at 3 and 12 months after the stroke by informant questionnaires, neuropsychological testing and clinical diagnosis. Cardiovascular risk factors, brain imaging and stroke features were analyzed using regression models to establish determinants for poststroke CI. RESULTS: A total of 164 patients (mean age = 72 +/- 7.5 years) were recruited. Out of 122 patients (74%) evaluated at 3 months, 81 (66%) had CI. Out of 101 patients (62%) evaluated at 12 months, 39 (39%) had CI no dementia, and 22 (22%) were demented. The new-onset dementia frequency at 1 year was 16%. Independent determinants for dementia were higher functional impairment at hospital egress (OR = 4.0), left-hemisphere large-vessel infarction (OR = 6.9) and a larger amount of white matter changes (OR = 1.3). CONCLUSIONS: In this first study on poststroke CI in Latin America, the frequencies and determinants of poststroke CI were similar to those in other cohorts of different ethnic origin.

MOV DISORD. 2010 NOV 15;25(15):2665-9.

IMPAIRED SENSE OF SMELL AND COLOR DISCRIMINATION IN MONOGENIC AND IDIOPATHIC PARKINSON'S DISEASE.

Kertelge L, Brüggemann N, Schmidt A, Tadic V, Wisse C, Dankert S, Drude L, van der Vegt J, Siebner H, Pawlack H, Pramstaller PP, **Behrens MI**, Ramirez A, Reichel D, Buhmann C, Hagenah J, Klein C, Lohmann K, Kasten M.

Olfaction is typically impaired in idiopathic Parkinson's disease (IPD), but its role is uncertain in monogenic PD. Diminished color discrimination has been suggested as another early sign of dopaminergic dysfunction but not been systematically studied. Furthermore, it is unknown whether both deficits are linked. We examined 100 patients with IPD, 27 manifesting mutation carriers (MC), 20 nonmanifesting mutation carriers (NMC), and 110 controls. Participants underwent a standardized neurological examination, the University of Pennsylvania Smell Identification Test (UPSIT), the Farnsworth-Munsell (FM) color discrimination test, and mutation testing in known PD genes. The monogenic group consisted of 15 Parkin (6MC/9NMC), 17 PINK1 (10MC/7NMC), 8 LRRK2 (4MC/4NMC), 3 SNCA (MC), and 4 ATP13A2 (MC) carriers. Olfaction was most impaired in IPD (UPSIT percentiles 10.1 ± 13.5) compared with all other groups (MC 13.8 ± 11.9, NMC 19.6 ± 13.0, controls 33.8 ± 22.4). Within MC, carriers of two mutations in Parkin and PINK1 showed higher UPSIT percentiles than LRRK2 and SNCA carriers. Color discrimination was reduced in IPD (FM total error score 134.8 ± 92.7). In MC (122.4 ± 142.4), the reduction was most pronounced in LRRK2, NMC (80.0 ± 38.8) were comparable with controls (97.2 ± 61.1). UPSIT and FM scores were correlated in the control (r = -0.305; P = 0.002) and the IPD group (r = -0.303; P = 0.006) but not among mutation carriers. First, we confirmed olfaction and color discrimination to be impaired in IPD and suggest olfaction to be a premotor sign. Second, olfaction differed between carriers with one and two mutations in Parkin/PINK1-associated PD. Third, olfaction and color discrimination impairment do not necessarily evolve in parallel.

ARQ BRAS CARDIOL. 2010 MAR;94(3):E28-30, E88-90.

ISCHEMIC STROKE AS THE FIRST MANIFESTATION OF SEVERE VENTRICULAR HYPERTRABECULATION/NON-COMPACTION.

Jaramillo A, Ramírez A, Galleguillos L, Vallejos J, **Illanes S.**

A rare congenital myocardial defect, known as left ventricular hypertrabeculation/non-compaction (LVHT), has been occasionally described associated with thrombus formation with a potential systemic embolic risk, but its association with ischemic strokes remains controversial. We report a case of ischemic stroke in a patient with severe LVHT and ventricular dysfunction as a possible etiologic synergistic association. In absence of other embolic sources, a severe LVTH associated with ventricular dysfunction could constitute a potential source of brain embolism, especially in patients with high suspicion of an embolic mechanism of ischemic stroke.

BRAIN RES. 2010 MAR 12;1320:135-42.

KINETICS OF HEMATOMA EXPANSION IN MURINE WARFARIN-ASSOCIATED INTRACEREBRAL HEMORRHAGE.

Illanes S, Zhou W, Heiland S, Markus Z, Veltkamp R.

BACKGROUND AND PURPOSE: The burden of intracerebral hemorrhage associated with oral anticoagulants (OAC-ICH) is growing. However, little is known about the pathophysiology of W-ICH. Herein, we refine a mouse model of OAC-ICH using repetitive T2* MRI to describe kinetics of hematoma enlargement, and establish a benchside point of care INR assay (PoC) for assessment of anticoagulation. METHODS: C57/BL6 mice drank warfarin (0.4mg/kg/24h) in their water. ICH was induced by stereotactic injection of collagenase type VII (0.045U) into the left striatum. Hemorrhagic blood volume was quantified by MRI T2* images and on cryosections 48h after ICH induction. Kinetics of hematoma expansion were compared in strongly, moderately, and non-anticoagulated mice using repeated MRI T2* imaging. The PoC INR technique was validated against standard laboratory INR, and tail vein bleeding time (TVBT). RESULTS: PoC INR correlated with central laboratory measurements ($r=0.989$; $p<0.0001$) and with TVBT ($r=0.982$; $p<0.0001$). Hematoma volume was 21.2+/-6.7mm(3) in heavily (PoC INR 4-5), 12.3+/-4.8 in moderately (INR 2-3), and 8.6+/-3.3 in non-anticoagulated mice (INR<1.2). Hematoma volume determined from cryosections and T2* MRI correlated well ($r=0.922$). Strength of anticoagulation was associated with neurologic outcome. Hematoma enlargement occurred mainly during the first 3h in anticoagulated mice. CONCLUSIONS: PoC allows repeated benchside INR measurements in individual mice which reflect the level of anticoagulation. Stronger anticoagulation results in larger hematoma volumes. As hematoma enlargement occurs mainly during the first hours, potential hemostatic therapies should be tested early in this OAC-ICH model.

ARCH NEUROL. 2010 JUN;67(6):670-6.

NONMOTOR SYMPTOMS IN GENETIC PARKINSON DISEASE.

Kasten M, Kertelge L, Brüggemann N, van der Vegt J, Schmidt A, Tadic V, Buhmann C, Steinlechner S, **Behrens MI**, Ramirez A, Binkofski F, Siebner H, Raspe H, Hagenah J, Lencer R, Klein C.

OBJECTIVES: To review current knowledge on nonmotor symptoms (NMS), particularly psychiatric features, in genetic Parkinson disease (PD) and to provide original data for genetic and idiopathic PD. DATA SOURCES: A MEDLINE search using Parkinson and known PD genes focused on the presence of depression, anxiety, hallucinations, and dementia was performed. Original data from 82 outpatients with idiopathic ($n = 55$) and genetic ($n = 27$) PD were obtained. STUDY SELECTION: All studies including information on NMS and patients with genetic PD. DATA EXTRACTION: Study methods and clinical and genetic information were summarized. DATA SYNTHESIS: The literature search yielded 1855 citations; 305 included genetic information on PD patients, of which 119 also contained information on any type of NMS (990 cases). Availability of information varied by gene and type of NMS; studies differed by recruitment and examination method. Literature search and original data showed high frequencies of the following NMS: depression, 8% to 37% (literature) and 33% to 40% (our data); anxiety, 7% to 37% (literature) and 10% to 22% (our data); hallucinations, 3% to 23% (literature) and 23% to 29% (our data); and dementia, 5% to 26% (literature), absent in our own data. CONCLUSIONS: Data on NMS in genetic PD are limited. Specific data needs include a systematic approach to NMS assessment reporting permitting comparability of studies. Overall, the frequency of NMS in genetic PD does not appear to be higher and may even be lower than in idiopathic PD. Nonmotor symptoms have a high impact on the patients' quality of life and caregiver burden and should be considered important and often treatable concomitant features of genetic PD.

ARCH NEUROL. 2010 NOV;67(11):1357-63.

RECESSIVELY INHERITED PARKINSONISM: EFFECT OF ATP13A2 MUTATIONS ON THE CLINICAL AND NEUROIMAGING PHENOTYPE.

Brüggemann N, Hagenah J, Reetz K, Schmidt A, Kasten M, Buchmann I, Eckerle S, Bähre M, Münchau A, Djarmati A, van der Vegt J, Siebner H, Binkofski F, Ramirez A, **Behrens MI**, Klein C.

OBJECTIVE: To determine clinical features and to identify changes in brain structure and function in compound heterozygous and heterozygous ATP13A2 mutation carriers. DESIGN: Prospective multimodal clinical and neuroimaging study.
SETTING: University of Lübeck, Lübeck, Germany. PARTICIPANTS: Eight family members of a large Chilean pedigree with Kufor-Rakeb syndrome (KRS). INTERVENTIONS: Clinical characterization, dopamine transporter (DAT) imaging, voxel-based morphometry (VBM), and transcranial sonography (TCS). MAIN OUTCOME MEASURES: Frequency of parkinsonian signs, brain structure, and functional alterations. RESULTS: The only available patient with compound heterozygous KRS showed a markedly reduced striatal DAT density bilaterally. Magnetic resonance imaging revealed severe global brain atrophy as well as iron deposition in the basal ganglia. The heterozygous mother had definite parkinsonism with reduced DAT density in

both putamina. While all asymptomatic heterozygous siblings displayed subtle extrapyramidal signs, DAT imaging revealed striatal tracer uptake within physiological levels. Voxel-based morphometry revealed an increase in gray matter volume in the right putamen and a decrease in the cerebellum of the heterozygous carriers. In all mutation carriers, the substantia nigra had a normal appearance on TCS. CONCLUSIONS: Single ATP13A2 heterozygous mutations may be associated with clinical signs of parkinsonism and contribute to structural and functional brain changes. Lack of hyperechogenicity in the substantia nigra may be a distinctive feature of this form of genetic parkinsonism. This, along with the finding of iron in the basal ganglia in our patient with KRS, implies a different underlying pathophysiology compared with other monogenic forms of parkinsonism and idiopathic PD and may place KRS among the syndromes of neurodegeneration with brain iron accumulation (NBIA).

NEUROBIOL DIS. 2010 SEP;39(3):402-8.

STRUCTURAL IMAGING IN THE PRESYMPTOMATIC STAGE OF GENETICALLY DETERMINED PARKINSONISM.

Reetz K, Tadic V, Kasten M, Brüggemann N, Schmidt A, Hagenah J, Pramstaller PP, Ramirez A, **Behrens MI**, Siebner HR, Klein C, Binkofski F.

Several genes associated with monogenic forms of Parkinson's disease (PD) have been discovered, opening up new avenues for the investigation of presymptomatic stages of PD. Using voxel-based morphometry in 30 asymptomatic mutation carriers (MC) with mutations in four different genes for PD and 100 healthy controls, we identified an increase in gray matter volume (GMV) in the striatum in asymptomatic Parkin, PINK1, ATP13A2 and, to a much lesser extent, in LRRK2 MC. Moreover, an increase in GMV was found in the parieto-temporo-occipital association cortex in asymptomatic Parkin and ATP13A2 MC. The observed striatal GMV increase might be the common structural correlate of compensatory mechanisms due to the latent dopaminergic deficit, reflecting the different, but probably interrelated pathogenic pathways resulting in nigral cell death. Asymptomatic PINK1 and LRRK2 MC also revealed smaller GMV in the hippocampal region, which might play a role in the observed psychiatric disorders.

HEADACHE. 2010 JAN;50(1):143-5.

SUNCT RESPONSIVE TO PERCUTANEOUS BALLOON COMPRESSION OF THE GASSERIAN GANGLION--10-YEAR FOLLOW-UP.

Baabor M, Rosas CS, Pérez-Limonte L.

We report the case of a woman with short-lasting unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) whose severe headache attacks ceased after percutaneous balloon compression of the Gasserian ganglion. The patient remains pain free after 10-year follow-up. This may be the first literature report of SUNCT in Chile.

INT REV NEUROBIOL. 2010;90:147-56.

TRANSCRANIAL SONOGRAPHY IN THE DISCRIMINATION OF PARKINSON'S DISEASE VERSUS VASCULAR PARKINSONISM.

Venegas-Francke P.

Cerebro-vascular disease is a well-known cause of parkinsonism. However, so far, there are no standardized clinical criteria that allow the diagnosis with accuracy and reliability. Rather, there is a great symptom overlap between idiopathic Parkinson's disease, other causes for parkinsonism, and vascular parkinsonism. Therefore, additional instruments are necessary to improve diagnostic accuracy. Transcranial sonography of brain parenchyma (TCS) has become a broadly applied tool in the diagnosis of Parkinson's disease, and secondary and atypical parkinsonian syndromes. In contrast to patients with idiopathic Parkinson's disease, patients with vascular parkinsonism in general show no hyperechogenicity of the substantia nigra. In contrast to a number of patients with atypical parkinsonian syndromes, also the basal ganglia are usually normoechogenic on TCS. A more specific approach to vascular parkinsonism includes the Doppler or duplex technique in order to show stenosis of vessels. Therefore, the combination of TCS and Doppler/duplex imaging might help to improve diagnosis of vascular parkinsonism transcranial.

DEPARTAMENTO DE OFTALMOLOGÍA

MOL VIS. 2010 AUG 13;16:1601-9.

DIFFERENT PHENOTYPES OF LATTICE CORNEAL DYSTROPHY TYPE I IN PATIENTS WITH 417C>T (R124C) AND 1762A>G (H572R) MUTATIONS IN TGFBI (BIGH3).

Romero P, Moraga M, Herrera L.

PURPOSE: To describe clinical data and to characterize mutations in the transforming growth factor beta-induced (TGFBI) gene in patients from three unrelated Chilean families with lattice corneal dystrophy type I (LCDI). METHODS: Snellen acuity tests, anterior segment slit lamp examinations, dilated fundus evaluations, and tonometry were performed for seven patients--five females and two males belonging to three unrelated families--affected with lattice corneal dystrophy Type I. Genomic DNA was also extracted from peripheral leukocytes from the seven patients and four healthy relatives. The 417C>T mutation (R124C) was screened using PCR-RFLP for the seven patients and four healthy relatives. Exons 11, 12, 13, and 14 were sequenced in one patient not carrying the mutation in codon 124. Comparison of phenotype to genotype was performed. RESULTS: The seven patients studied exhibited LCDI in both eyes, most of which were symmetric. Affected individuals demonstrated progression from central subepithelial needlelike deposits and polymorphic anterior stromal opacities. The age at onset of symptoms varied between six to 15 years old in Family One; the patient in Family Two was five years old and the patient in Family Three was 21 years old. Visual acuity varied from 1.0 to 0.05. Two patients, aged 50 and 45 years, underwent penetrating keratoplasty in both eyes, and two patients, aged 47 and 24 years, underwent penetrating keratoplasty in one eye. The only patient in Family Three exhibited a somewhat distinct phenotype, with yellowish discoloration in the anterior stroma and fewer, but thicker lattice lines than the patients in Families One and Two. Screening for the mutation C>T at the nucleotide position 417 (R124C) in exon 4 in the three families revealed the heterozygous R124C mutation in Families One and Two. In Family Two, the mutation was a de novo mutation, as neither parent was a carrier. Screening by sequencing analysis for mutation in exons 11, 12, 13, and 14 in the affected patient in Family Three revealed a heterozygous A1762G mutation (H572R) in exon 13. CONCLUSIONS: This is the second report of the 417C>T mutation and the first report of 1762 A>G mutation (H572R) in Chilean patients. The H572R mutation identified is associated with a distinct lattice corneal dystrophy type I phenotype.

DEPARTAMENTO DE OTORRINOLARINGOLOGÍA

J PHYSIOL PARIS. 2010 MAY-SEP;104(3-4):190-6.

A VISUAL CUE MODULATES THE FIRING RATE AND LATENCY OF AUDITORY-CORTEX NEURONS IN THE CHINCHILLA.

Delano PH, Elgueda D, Ramirez F, Robles L, Maldonado PE.

We studied single and multi-unit activity recorded with tetrodes, from the left auditory cortex of awake chinchillas while they performed a frequency discrimination task. Auditory stimuli were preceded by a silent visual cue. We examined firing rates and first-spike latencies of 181 units in the presence and absence of the visual cue. To discard possible auditory artifacts produced by the visual cue, cochlear potentials were simultaneously recorded by an electrode positioned at the round window of the right cochlea. We found that the visual stimulus altered the firing rate and the mean first-spike latency of 9% and 18% of the recorded auditory-cortex cells, respectively. Furthermore, we found that the subset of neurons in which the firing rate was modulated by the visual cue was distinct from the subset of neurons that changed their latency in the presence of the visual cue. Adding both groups, a visual-stimulus modulated the firing characteristics of 27% of the recorded auditory-cortex neurons in the awake chinchilla. Our results imply that in the auditory cortex, latency and firing rate can be independently altered by visual stimuli, and that both types of analysis must be considered in order to fully understand neural cross-modal interactions.

DEPARTAMENTO DE OBSTETRICIA Y GINECOLOGÍA

LABORATORIO ENDOCRINOLOGÍA

MOL MED. 2010 MAR;16(3-4):129-36.

CHANGES IN THE EXPRESSION OF INSULIN SIGNALING PATHWAY MOLECULES IN ENDOMETRIA FROM POLYCYSTIC OVARY SYNDROME WOMEN WITH OR WITHOUT HYPERINSULINEMIA.

Fornes R, Ormazabal P, Rosas C, Gabler F, **Vantman D, Romero C, Vega M.**

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder associated with insulin resistance and compensatory hyperinsulinemia. Scarce information is available on the expression of molecules involved in the insulin pathway in endometria from women with PCOS. Therefore, we examined the protein levels of insulin-signaling molecules, like insulin receptor, insulin-receptor substrate (IRS)-1, pIRS-1Y612, Akt, AS160, pAS160T642 and GLUT4 in endometria from PCOS women with or without hyperinsulinemia. Protein levels were assessed by Western blot and immunohistochemistry in 21 proliferative-phase endometria from control women (CE = 7), normoinssulinemic PCOS women (PCOSE-NI = 7) and hyperinsulinemic PCOS women (PCOSE-HI = 7). The data show no differences in the expression of insulin receptor between all groups as assessed by Western blot; however, IRS-1 and pIRS-1Y612 were lower in PCOSE-HI than controls and PCOSE-NI ($P < 0.05$). AS160 was detected in all analyzed tissues with similar expression levels between groups. Importantly, PCOSE-HI exhibited lower levels of pAS160T642 ($P < 0.05$) and of GLUT4 ($P < 0.05$) compared with CE. The immunohistochemistry for insulin receptor, IRS-1, Akt, AS160 and GLUT4 showed epithelial and stromal localization; IRS-1 staining was lower in PCOSE-HI ($P < 0.05$). In conclusion, human endometrium has the machinery for glucose uptake mediated by insulin. The diminished expression of GLUT4, as well as the lower level of pIRS-1Y612 and pAS160T642 exhibited by PCOSE-HI, suggests a disruption in the translocation of vesicles with GLUT4 to the cell surface in these patients.

HUM REPROD. 2010 NOV;25(11):2870-7.

LEVELS OF RABS AND WAVE FAMILY PROTEINS ASSOCIATED WITH TRANSLOCATION OF GLUT4 TO THE CELL SURFACE IN ENDOMETRIA FROM HYPERINSULINEMIC PCOS WOMEN.

Rosas C, Gabler F, **Vantman D, Romero C**, **Vega M**.

BACKGROUND: Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder highly associated with insulin resistance and compensatory hyperinsulinemia. It is known that the insulin signaling pathway is impaired in endometria from PCOS hyperinsulinemic women, but no information is available about molecules associated with cell surface GLUT4 translocation. We therefore evaluated the protein levels of AS160 target molecules, Rab8A and Rab10, and the WAVE family proteins involved in the cortical-actin remodeling, Neural Wiskott-Aldrich Syndrome Protein (N-WASP) and WASP, in endometria from hyperinsulinemic PCOS women and controls. METHODS: Protein levels were assessed by western blot, immunohistochemistry and immunofluorescence in proliferative (PE = 7) and secretory (SE = 7) phase endometria from control women and in endometria from hyperinsulinemic PCOS women (PCOS h-INS = 7). RESULTS: Similar levels were detected for Rab10 in the three studied groups; however, Rab8A levels decreased in SE ($P < 0.05$) while higher levels were obtained in PCOSE h-INS compared with PE ($P < 0.05$). In the normal menstrual cycle, Neural Wiskott-Aldrich syndrome protein (N-WASP) and WASP levels were increased in SE versus PE ($P < 0.05$), but in PCOSE h-INS, the levels were diminished compared with PE ($P < 0.05$). CONCLUSIONS: SE is characterized by protein expression changes associated with glucose uptake. In endometria from PCOS women with hyperinsulinemia, reduced levels of WAVE family proteins could compromise the cell surface GLUT4 exposure and the consequent glucose uptake in this tissue.

REPRODUCTION. 2010 JUL;140(1):123-31.

ROLE OF THE TRANSCRIPTIONAL FACTORS FOXO1 AND PPARG ON GENE EXPRESSION OF SLC2A4 IN ENDOMETRIAL TISSUE FROM WOMEN WITH POLYCYSTIC OVARY SYNDROME.

Kohan K, **Carvajal R**, Gabler F, **Vantman D, Romero C, Vega M.**

Fifty to seventy percent of patients with polycystic ovary syndrome (PCOS) present hyperinsulinemia. On the other hand, reports indicate that forkhead box class O 1 (FOXO1) and peroxisome proliferator-activated receptor-gamma (PPARG) are involved in the insulin signaling pathway, regulating the gene expression of SLC2A4 (GLUT4). The negative effect of FOXO1 over PPARG transcription disappears when FOXO1 is phosphorylated (p-FOXO1) and excluded from the nucleus, whereas PPARG can suppress gene expression of SLC2A4. Scarce knowledge is available in endometrium of women with PCOS and hyperinsulinemia (PCOSE h-Ins) about the role of these factors. We aimed to evaluate whether the endocrine and metabolic

status of PCOS modify the levels of gene and protein expression of FOXO1, PPARG, and SLC2A4 in the endometria from hyperinsulinemic PCOS women compared with controls. In endometria from control (CE, n=7) or PCOSE h-Ins (n=7), we determined the subcellular location and protein levels of p-FOXO1Ser319 and FOXO1/FOXO4 by immunohistochemistry and western blot respectively; gene and/or protein levels of PPARG and SLC2A4 were evaluated by RT-PCR and/or western blot. Cytoplasm location for FOXO1 and p-FOXO1Ser319 was immunodetected in both groups of endometria, showing significantly higher staining in PCOSE h-Ins for these proteins (P<0.05). In PCOSE h-Ins, gene and protein levels of PPARG were significantly higher than in CE, whereas SLC2A4 mRNA was decreased (P<0.05). In conclusion, the derepression of PPARG transcription by the high levels of p-FOXO1Ser319 could partially account for the lower levels of SLC2A4 found in PCOSE h-Ins, suggesting an alteration of the endometrial function in these patients.

STEROIDS. 2010 DEC;75(12):810-7.

THE CONVERSION OF DEHYDROEPIANDROSTERONE INTO ANDROST-5-ENE-3BETA,17BETA-DIOL (ANDROSTENEDIOL) IS INCREASED IN ENDOMETRIA FROM UNTREATED WOMEN WITH POLYCYSTIC OVARIAN SYNDROME.

Plaza F, Gabler F, **Romero C, Vantman D**, Valladares L, **Vega M.**

The changes in endometrial homeostasis found in women with polycystic ovarian syndrome (PCOS) could be associated with alterations in the intracrine metabolism of steroid hormones. The uptake of dehydroepiandrosterone-sulphate (DHEA-S), precursor of the intracrine pathway, is achieved by transporters, such as organic anion transporter polypeptides (OATPs), and molecules with oestrogenic activity, such as androst-5-ene-3beta,17beta-diol (androstenediol), can be generated. We aimed to determine androstenediol generation and the expression of OATPs in human endometria throughout the menstrual cycle and in endometria from PCOS women. Endometrial samples were obtained from control women in the proliferative phase (control endometria (CEp), n=7), secretory phase (CEs, n=7), and from PCOS patients (PCOSEp, n=7). The mRNA levels of OATP-B, OATP-D and OATP-E were measured by reverse transcriptase polymerase chain reaction (RT-PCR) and protein levels of OATP-E by immunofluorescence; 3beta-hydroxysteroid dehydrogenase (HSD) by immunohistochemistry/Western blot; the metabolism of DHEA to androstenediol was evaluated by thin layer chromatography-high-performance liquid chromatography (TLC-HPLC). Lower levels of OATP-E transcript were obtained in PCOSEp ($p<0.05$) compared with CEp, while OATP-E protein levels ($p<0.05$) and DHEA conversion to androstenediol ($p<0.01$) were higher in PCOSEp. Lower 3beta-(hydroxysteroid dehydrogenase) HSD protein levels were found in PCOSEp ($p<0.05$) (Western blot, immunohistochemistry). These results reveal a higher capacity of the endometria from PCOS women to metabolise DHEA to androstenediol, which, coupled with the high oestrogen sensitivity previously found in these endometria, may account for the increase in cell proliferation in PCOSEp already reported.

DEPARTAMENTO DE OFTALMOLOGÍA

MOL VIS. 2010 AUG 13;16:1601-9.

DIFFERENT PHENOTYPES OF LATTICE CORNEAL DYSTROPHY TYPE I IN PATIENTS WITH 417C>T (R124C) AND 1762A>G (H572R) MUTATIONS IN TGFBI (BIGH3).

Romero P, Moraga M, Herrera L.

PURPOSE: To describe clinical data and to characterize mutations in the transforming growth factor beta-induced (TGFBI) gene in patients from three unrelated Chilean families with lattice corneal dystrophy type I (LCDI). METHODS: Snellen acuity tests, anterior segment slit lamp examinations, dilated fundus evaluations, and tonometry were performed for seven patients--five females and two males belonging to three unrelated families--affected with lattice corneal dystrophy Type I. Genomic DNA was also extracted from peripheral leukocytes from the seven patients and four healthy relatives. The 417C>T mutation (R124C) was screened using PCR-RFLP for the seven patients and four healthy relatives. Exons 11, 12, 13, and 14 were sequenced in one patient not carrying the mutation in codon 124. Comparison of phenotype to genotype was performed. RESULTS: The seven patients studied exhibited LCDI in both eyes, most of which were symmetric. Affected individuals demonstrated progression from central subepithelial needlelike deposits and polymorphic anterior stromal opacities. The age at onset of symptoms varied between six to 15 years old in Family One; the patient in Family Two was five years old and the patient in Family Three was 21 years old. Visual acuity varied from 1.0 to 0.05. Two patients, aged 50 and 45 years, underwent penetrating keratoplasty in both eyes, and two patients, aged 47 and 24 years, underwent penetrating keratoplasty in one eye. The only patient in Family Three exhibited a somewhat distinct phenotype, with yellowish discoloration in the anterior stroma and fewer, but thicker lattice lines than the patients in Families One and Two. Screening for the mutation C>T at the

nucleotide position 417 (R124C) in exon 4 in the three families revealed the heterozygous R124C mutation in Families One and Two. In Family Two, the mutation was a de novo mutation, as neither parent was a carrier. Screening by sequencing analysis for mutation in exons 11, 12, 13, and 14 in the affected patient in Family Three revealed a heterozygous A1762G mutation (H572R) in exon 13. CONCLUSIONS: This is the second report of the 417C>T mutation and the first report of 1762 A>G mutation (H572R) in Chilean patients. The H572R mutation identified is associated with a distinct lattice corneal dystrophy type I phenotype.

DEPARTAMENTO DE PSIQUIATRÍA Y SALUD MENTAL

PSYCHIATR GENET. 2010 FEB;20(1):25-30.

FLUOXETINE RESPONSE IN IMPULSIVE-AGGRESSIVE BEHAVIOR AND SEROTONIN TRANSPORTER POLYMORPHISM IN PERSONALITY DISORDER.

Silva H, Iturra P, Solari A, Villarroel J, Jerez S, Jiménez M, Galleguillos F, Bustamante ML.

BACKGROUND: Disturbances in central serotonin function have been implicated in impulsive and aggressive behavior. A deletion/insertion polymorphism within the 5-HT transporter promoter gene (5-HTTLPR) is thought to be associated with disturbed impulse control, anxiety, and depression. The serotonin transporter (5-HTT) is the primary action site for selective serotonin reuptake inhibitors (SSRIs). Several studies of major depression have shown that the l allele of 5-HTTLPR is associated with better SSRI antidepressant effects than the s allele. METHODS: This study investigates the association between response of impulsivity to treatment with fluoxetine and 5-HTTLPR polymorphism in 49 personality disordered patients. Additionally, we studied TPH1, 5HT1B and 5HT2C receptor polymorphisms as predictors of response in this population. RESULTS: Results reveal that patients with the l/l genotype of 5-HTTLPR had a significantly better response to fluoxetine when compared to s allele carriers, as evaluated on the basis of total ($P<0.05$) and Aggression subscale ($P<0.01$) Overt Aggression Scale Modified-score percentage change. There were no significant associations between fluoxetine response and TPH1 (A218C) (-6525 A>G) (-5806 G>T), HTR1B (G861C) and HTR2C (G68C) genotype groups. CONCLUSION: This is the first study assessing the association between these polymorphisms and anti-impulsive response to fluoxetine in personality disorder. As the s genotype is associated with a poorer selective serotonin reuptake inhibitors response in major depression, bulimia nervosa and borderline personality disorder, it could represent a common biological background for SSRI response.

ACTAS ESP PSIQUIATR. 2010 NOV-DEC;38(6):358-64.

SLEEP DISORDERS IN THE ADULT POPULATION OF SANTIAGO OF CHILE AND ITS ASSOCIATION WITH COMMON PSYCHIATRIC DISORDERS.

Fritsch Montero R, Lahsen Martínez P, Romeo Gómez R, Araya Baltra R, **Rojas Castillo G.**

INTRODUCTION: Sleep disorders are a frequent problem and they are a usual reason of primary care consultation, because they cause a significant deterioration in the quality of life. Insomnia is the most common sleep disorder and it has a total prevalence in adults estimated of 19.1%, of whom 85% are chronic insomnia, which in turn is closely related to psychiatric disorders and even more it has been described as a depressive episode marker. AIMS: To characterize the Santiago adult population suffering from sleep disorders and analyze their statistical association with common mental disorders. METHODOLOGY: It corresponds to a secondary analysis of the survey "Common Mental Disorders in Santiago". A cross-sectional survey that used as a sampling frame the adult population of Santiago aged between 16 to 64 years was carried out. A structured interview covering sociodemographic factors and the Revised Clinical Interview Schedule (CIS-R) to measure emotional symptoms, were applied. RESULTS: 3867 people representative of the adult population were evaluated (52.3% women, 47.7% men). The prevalence of sleep disorders was 26.3%. Sociodemographic risk factors, statistically significants, were detected like female gender, unemployed seeking employment, the presence of a common mental disorder, alcohol and drugs consumption in the last month, among others. CONCLUSIONS: There is a high prevalence of sleep disorders among the population of Santiago; this is closely associated to female gender, social disadvantages and potently to the presence of a common mental disorder.

AM J RESPIR CRIT CARE MED. 2010 MAR 15;181(6):578-86.

LUNG OPENING AND CLOSING DURING VENTILATION OF ACUTE RESPIRATORY DISTRESS SYNDROME.

Caironi P, Cressoni M, Chiumello D, Ranieri M, Quintel M, Russo SG, **Cornejo R**, Bugedo G, Carlesso E, Russo R, Caspani L, Gattinoni L.

RATIONALE: The effects of high positive end-expiratory pressure (PEEP) strictly depend on lung recruitability, which varies widely during acute respiratory distress syndrome (ARDS). Unfortunately, increasing PEEP may lead to opposing effects on two main factors potentially worsening the lung injury, that is, alveolar strain and intratidal opening and closing, being detrimental (increasing the former) or beneficial (decreasing the latter). OBJECTIVES: To investigate how lung recruitability influences alveolar strain and intratidal opening and closing after the application of high PEEP. METHODS: We analyzed data from a database of 68 patients with acute lung injury or ARDS who underwent whole-lung computed tomography at 5, 15, and 45 cm H(2)O airway pressure. MEASUREMENTS AND MAIN RESULTS: End-inspiratory nonaerated lung tissue was estimated from computed tomography pressure-volume curves. Alveolar strain and opening and closing lung tissue were computed at 5 and 15 cm H(2)O PEEP. In patients with a higher percentage of potentially recruitable lung, the increase in PEEP markedly reduced opening and closing lung tissue ($P < 0.001$), whereas no differences were observed in patients with a lower percentage of potentially recruitable lung. In contrast, alveolar strain similarly increased in the two groups ($P = 0.89$). Opening and closing lung tissue was distributed mainly in the dependent and hilar lung regions, and it appeared to be an independent risk factor for death (odds ratio, 1.10 for each 10-g increase). CONCLUSIONS: In ARDS, especially in patients with higher lung recruitability, the beneficial impact of reducing intratidal alveolar opening and closing by increasing PEEP prevails over the effects of increasing alveolar strain.

BMJ CASE REPORTS 2010; DOI:10.1136/BCR.02.2010.2708.

ORGANIZING PNEUMONIA IN PATIENTS WITH SEVERE RESPIRATORY FAILURE DUE TO NOVEL A (H1N1) INFLUENZA.

Rodrigo Cornejo, Osvaldo Llanos, Cristina Fernández, Juan Carlos Díaz, Gonzalo Cardemil, Jorge Salguero, Cecilia Luengo, Eduardo Tobar, Carlos Romero, Luis Ricardo Gálvez.

The authors describe two cases that developed organizing pneumonia (OP) associated with novel influenza A(H1N1) virus. These patients were admitted to intensive care unit (ICU) because of severe respiratory failure. After initial clinical improvement, both patients worsened their condition during their second week of ICU stay, presenting fever, increasing in inflammatory parameters and worsening in oxygen exchange and respiratory mechanics. Chest x-rays and computed tomographies showed an increment on lung infiltrates, given by areas of consolidation and ground glass opacification. Although broad-spectrum antibiotics were administered, patients showed no improvement. All cultures, including bronchoalveolar lavage samples, were negative. In both cases, an open lung biopsy was performed, and histopathological examination of the specimen was compatible with OP. Both patients were successfully treated with high-dose corticoids. The aim of this report is to alert about the possibility of OP associated with novel influenza virus in patients with severe respiratory failure.

J CRIT CARE. 2010 DEC 1.

PERSISTENT SEPSIS-INDUCED HYPOTENSION WITHOUT HYPERLACTATEMIA: IS IT REALLY SEPTIC SHOCK?

Hernandez G, Castro R, **Romero C**, de la Hoz C, Angulo D, Aranguiz I, Larrondo J, Bujes A, Bruhn A.

PURPOSE: The prognostic value of hyperlactatemia in septic shock is unquestionable. However, as current definitions do not include hyperlactatemia as a mandatory criterion, some hypotensive patients may be diagnosed as having septic shock despite exhibiting normolactatemia. The significance of persistent sepsis-induced hypotension without hyperlactatemia is unclear. Is it really septic shock? Our aim was to determine differences in outcome between patients diagnosed as having septic shock but exhibiting normal vs elevated lactate levels during evolution. We also explored the potential implications of including hyperlactatemia as an obligatory diagnostic criterion. METHODS: We performed retrospective analyses on a cohort of 302 septic shock patients. RESULTS: When we divided patients according to the presence of hyperlactatemia, 34% evolved without hyperlactatemia and exhibited a very low mortality risk (7.7% compared with 42.9% of those with hyperlactatemia). These patients also presented less severe organ dysfunctions and higher central venous O(2) saturation values, and required lower norepinephrine doses. The potential inclusion of hyperlactatemia in septic shock definition would reduce incidence in 34% but increase absolute mortality risk in 11%. CONCLUSIONS: Persistent sepsis-induced hypotension without hyperlactatemia may not constitute a real septic shock. Our results support the need to review the current definition of septic shock. Hyperlactatemia could represent an objective parameter worth to be explored as a potential diagnostic criterion for septic shock.

CHEST. 2010 JUN;137(6):1278-82.

SWALLOWING DYSFUNCTION IN NONNEUROLOGIC CRITICALLY ILL PATIENTS WHO REQUIRE PERCUTANEOUS DILATATIONAL TRACHEOSTOMY.

Romero CM, Marambio A, Larrondo J, Walker K, Lira MT, **Tobar E, Cornejo R, Ruiz M.**

BACKGROUND: The aim of this study was to determine the incidence of swallowing dysfunction in nonneurologic critically ill patients who require percutaneous dilatational tracheostomy (PDT) for prolonged mechanical ventilation (MV) and to compare the duration of the cannulation period and length of stay in the critical care unit (CCU) in patients with and without swallowing dysfunction. METHODS: A total of 40 consecutive patients without neurologic disorders who require PDT for prolonged MV were included. Previous to the tracheostomy decannulation process, an otolaryngologist performed a fiberoptic endoscopic evaluation of swallowing (FEES). We used analysis of variance for the analysis; the results are presented as mean values +/- SD. RESULTS: Mean age was 62 +/- 15 years. Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were 21 +/- 2 and 9 +/- 1, respectively. Time of MV previous to PDT was 20 +/- 11 days, total MV duration was 38 +/- 16 days, and CCU stay was 63 +/- 27 days. The incidence of swallowing dysfunction in this group of patients was 38% (15/40). No difference was found in the age or time period of MV previous to PDT between groups. The time period between FEES to tracheostomy decannulation process was 19 +/- 11 days in patients with swallowing dysfunction vs 2 +/- 4 days in those patients without dysfunction ($P < .001$). Patients who developed swallowing dysfunction stayed longer in the CCU (69 +/- 23 vs 47 +/- 19 days, $P < .01$). CONCLUSIONS: Nearly 40% of nonneurologic critically ill patients requiring PDT for prolonged MV presented swallowing dysfunction and experienced a significant delay in their tracheostomy decannulation process.

OFICINA DE APOYO A LA INVESTIGACIÓN CLÍNICA

INFLAMM BOWEL DIS. 2010 JUL;16(7):1097-107.

CHARACTERIZATION OF THE NOVEL ST2/IL-33 SYSTEM IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE.

Beltrán CJ, Núñez LE, Díaz-Jiménez D, Farfan N, Candia E, Heine C, López F, González MJ, Quera R, Hermoso MA.

BACKGROUND: ST2 has been proposed to be a regulator of inflammation and Th1/Th2 balance. ST2L is the IL-33 membrane receptor and belongs to the IL-1R family. The soluble variant, ST2s, is identical to the extracellular region of ST2L and competes for IL-33 binding, inhibiting receptor signaling. Although ST2s has been associated with inflammatory processes in patients with sepsis, trauma, asthma, and autoimmunity, until now there are no reported studies showing the role of ST2/IL-33 in inflammatory bowel disease (IBD). METHODS: Expression of ST2 and IL-33 was determined in serum and colonic biopsies from IBD patients. ST2 transcript and protein was determined by reverse-transcription polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA)/immunoblot, respectively, and IL-33 protein by ELISA. Intestinal mucosa localization of ST2 and IL-33 was conducted by immunofluorescence. RESULTS: ST2s transcript in the colonic mucosa was mainly expressed in UC patients rather than Crohn's disease or control; however, ST2L mRNA remained constant in all samples. Total ST2 protein was significantly higher in mucosa samples from patients with active UC, with a predominant induction of ST2s that strongly correlates with serum ST2 levels. Mucosa IL-33 levels were higher in UC patients and serum levels were barely detected in all patient groups. ST2 and IL-33 are both abundantly expressed in the cytoplasm of epithelial cells of control subjects; however, in ulcerative colitis patients ST2 decreases and IL-33 showed cytoplasm-nuclear redistribution. CONCLUSIONS: The novel association between the ST2/IL-33 system and IBD seems to identify that variations in this axis might regulate the inflammatory process in these diseases

IMMUNOL CELL BIOL. 2010 AUG 17.

INTERLEUKIN 10 DECREASES MICA EXPRESSION ON MELANOMA CELL SURFACE.

Serrano AE, Menares-Castillo E, Garrido-Tapia M, Ribeiro CH, Hernández CJ, Mendoza-Naranjo A, Gatica-Andrades M, Valenzuela-Diaz R, Zúñiga R, **López MN**, Salazar-Onfray F, Aguillón JC, Molina MC.

Natural-killer group 2, member D (NKG2D) binds to a variety of ligands, including the major histocompatibility complex (MHC) class I chain-related proteins (MIC) and UL16-binding proteins (ULBP). It is regarded as a co-activating receptor on NK cells, having an important role in the cell-mediated immune response to tumours. We studied the influence of interleukin (IL)-10 on the regulation of MIC and ULBP expression on melanoma cells, and its effect on the cytotoxic function of NK cells in vitro.

Here, we show that, in the presence of IL-10, FMS mel and BL mel cell lines decreased MICA and ULBP2 surface expression, whereas MHC class I did not change substantially on the cell surface. MICA mRNA levels decreased in IL-10-treated FMS and IL-10-transduced BL cell lines. Interestingly, we observed that MICB surface expression and its mRNA levels increased upon IL-10 treatment in a melanoma cell line. These changes in NKG2D ligands surface expression patterns owing to IL-10 treatment resulted in an effect on lysis susceptibility mediated by lymphocyte-activated killer cells, as tumour cell lines that displayed a higher decrease of MICA on their surface had lower levels of lysis. In addition, expression of CD107a was downregulated on the surface of NK cells following stimulation with IL-10-treated FMS cells. Our results suggest a novel function for IL-10 in the modulation of NKG2D ligand expression and in the control of cytotoxicity mediated by NKG2D/NKG2D ligand axis.Immunology and Cell Biology advance online publication, 17 August 2010; doi:10.1038/icb.2010.100.

TRANSPLANT PROC. 2010 JAN-FEB;42(1):381-6.

ISOLATION OF VIABLE PORCINE ISLETS BY SELECTIVE OSMOTIC SHOCK WITHOUT ENZYMATIC DIGESTION.

Atwater I, **Guajardo M,** Caviedes P, Jeffs S, Parrau D, Valencia M, **Romero C**, Arriagada C, Caamaño E, Salas A, Olguin F, Atlagich M, Maas R, Mears D, Rojas E.

Islet transplantation is a potential cure for type 1 diabetes, but clinical results have been disappointing. Currently, islet isolation is by enzymatic digestion of the pancreas which has significant pitfalls: warm ischemia exposure, collagenase-induced damage to the islet mass and viability, poor reproducibility, high cost, a relatively low number of islets obtained per whole pancreas, and selection of islets for collagenase resistance rather than for glucose responsiveness. In the present study we performed a series of experiments in a porcine model to demonstrate the feasibility of a new isolation method based on selective osmotic shock (SOS) using very high glucose solutions, doubling or tripling physiological osmotic strength. The SOS method can be carried out at room temperature or in the cold eliminating warm ischemia time which damages the islets. The SOS method does not depend on the texture of the pancreas so all pancreases can be processed identically and the process can be fully automated. The SOS method isolates all the islets of the pancreas regardless of size and shape allowing a greater number of islets to be harvested. The SOS method avoids exposure to toxins in collagenase solutions, is inexpensive and selects for islets with high concentrations of Glut 2 transporters, representing the best glucose responding islets. The SOS method showed a comparable recovery of islets from young pig pancreas and the islets showed improved viability. We conclude that the selective osmotic shock (SOS) method of separating islets from the pancreatic tissue is superior to the collagenase method.