duodenal lesion but was not deemed to be a candidate for therapeutic resection of the lesion, owing to her widely metastatic disease. The patient underwent palliative radiotherapy for her brain lesions and was put on prophylactic steroids, but she went through a rapidly downhill course and succumbed to her disease a few weeks later. **Discussion:** Malignant melanoma has the propensity to metastasize widely. Most reported cases of gastrointestinal metastases are those of mucosal or submucosal masses, serosal implants, or carcinomatosis, the most common form being multiple submucosal implants growing intraluminally to cause intestinal obstruction. However, many of these lesions can also ulcerate, resulting in occult or overt gastrointestinal bleeding. Although patients with gastrointestinal tract metastases from melanoma carry a dismal prognosis, many such patients can have palliation of symptoms by surgical resection with minimum morbidity and mortality. It is therefore important for clinicians to make an accurate and timely diagnosis of the cause of gastrointestinal bleeding in such patients to prevent rapidly fatal outcomes.

92

ADRENAL INSUFFICIENCY AS THE INITIAL PRESENTATION OF HIV DISEASE. P. Sircar, D. Godkar, J. Balachandran, S. Niranjan, Coney Island Hospital, Brooklyn, NY.

Introduction: Endocrine deficiencies, particularly functional abnormalities of the hypothalamopituitary-adrenal axis, are common in patients with human immunodeficiency virus (HIV) disease. In most cases, adrenal insufficiency, although present, is not enough to cause clinical symptoms. Few cases have been reported where adrenal insufficiency was the only complaint, or even more rarely, the presenting complaint of a patient with HIV disease, without evidence of any superimposed opportunistic infections. We present such a rare case, as we encountered at our hospital. **Case Report:** A 31-year-old African American male with no significant past medical history presented to the emergency room with 2 to 3 days of severe weakness, dizziness, fatigue, and vomiting. He was found to be hypotensive (blood pressure 70/50 mm Hg), the hypotension being refractory to fluid resuscitation. The patient was also hyperkalemic (potassium 5.5 mEq/L). Baseline cortisol was 5.1 mg/dL; stimulated value at the end of 1 hour with 250 μg of cosyntropin was 8.7 mg/dL. Extensive workup for sepsis was negative, and so were CMV, *Toxoplasma*, and cryptococcal antibody titers. CD4 count was 6/μL, and antibody to HIV-1 virus was positive, with a viral load of 450,000 copies/mL. The patient ultimately responded to stress doses of hydrocortisone(300 mg/d) during a hospital stay and was discharged on maintenance doses of 20 mg of hydrocortisone at am and 10 mg at pm. At 6 months of follow-up, the patient was doing well, and although it has not been possible to take him off steroids, he is currently on a maintenance dose of 10 mg at am and 5 mg at pm of hydrocortisone. **Discussion:** Various mechanisms have been proposed to explain the mechanism of adrenal insufficiency in HIV-positive individuals. More often than not, infective agents such as CMV, cryptococcus, human herpesvirus 8, and tuberculosis have been found to be the culprits. Many times, no definite etiology can be found, and such cases are usually attributed to HIV itself or some abnormal autoimmune process getting triggered in the face of generalized reduction in body immunity. Further research is needed to understand the true mechanism of adrenal insufficiency in such obscure cases. This rare case also serves as a reminder to clinicians to keep in mind the differential diagnosis of adrenal insufficiency as the presenting picture of acquired immune deficiency syndrome (AIDS), even when a background diagnosis of HIV positivity is absent.

93

CHIRAL SEPARATION OF THE INOTROPIC AND CHRONOTROPIC ACTIONS OF DIGOXIN IN A CANINE MODEL. C. Spies, A. Gupta, D. Glock, J. Spoon, L. Williams, V. Ranade, J. Snell, J. Molnar, J.C. Somberg, Rush University, Chicago, IL; Lake Bluff, IL.

The digoxin molecule is chiral, having asymmetries at the C3 + C17 carbon centers that give rise to stereoscopic isomers. The actions of digoxin chiral isolates on cardiac conduction and contractility have been shown to differ in the guinea pig. Additional supplies of the chiral isolates were obtained through HPLC employing a cyclobond chiral column, separating digoxin into two distinct chromatographic peaks, each with a different retention time. The optical rotation of the two isolates were +17 and +3, respectively, with the same mass/change ratio (m/z) of 780, identical to racemate digoxin. The effects of the isolates were determined in 15 catheterized dogs anesthetized with isoflurane. The effects of the two chiral isolates were contrasted to digoxin for changes in HR, PR, and AH intervals, as well as left and right ventricular dp/dt. Digoxin and the isolates were infused at 1.5 μg/kg/min. Digoxin racemate caused a 15% slowing in HR at 45 minutes, a 15% increase in PR interval at 60 minutes, and a 20% increase in AH interval at 75 minutes. Dp/dt_r was increased by 20% at 15 minutes and 50% at 60 minutes, whereas dp/dt_L by 20% at 15 minutes and 50% at 105 minutes. Chiral isolate 1 failed to decrease HR or increase PR or AH intervals by 15%. Dp/dt_r was increased by 50% at 15 minutes and dp/dt_L by 20% at 15 minutes and 50% at 30 minutes. Isolate 2 slowed HR by 15% at 15 minutes and PR by 15% at 30 minutes, and AH decreased by 20% at 15 minutes, whereas dp/dt_r was increased by 20% at 45 minutes and dp/dt_L by 20% at 75 minutes; a 50% augmentation was not obtained. The contractility/conduction index (dose to 20% increase in dp/dt ÷ dose to 20% increase in AH interval) was 0.2 digoxin, < 0.125 chiral 1 and 3 for chiral 2. There is a marked difference between isolates 1 and 2 in AV conduction and contractile augmentation ($p < .001$). Digoxin can be chirally separated, with one isolate causing progressive AV conduction delay and the other isolate predominantly causing contractile augmentation.

94

A CASE OF FULMINANT HEPATIC FAILURE TREATED WITH *N*-ACETYLCYSTEINE. J. Venkatesan, M. Soni, T. Schwartz, M. Bernstein, Coney Island Hospital, Brooklyn, NY.

Background: Fulminant hepatic failure is one of the most challenging gastrointestinal emergencies and encompasses a pattern of clinical symptoms and pathophysiologic responses associated with rapid arrest of normal hepatic function. Hyperacute hepatic failure usually presents with liver function abnormalities, coagulopathy, encephalopathy, and multisystem failure. This is a case report of hyperacute liver failure that presented with coagulopathy and an isolated elevation of aspartate aminotransferase and normal alanine aminotransferase. The etiology for liver failure is multifactorial. In our patient, the above presentation was attributed to therapeutic misadventure: acute acetaminophen toxicity in chronic alcoholics at a very low dose. The patient had improvement of symptoms and liver function after treatment with *N*-acetylcysteine. **Case Report:** A 51-year-old male with a past medical history of hypertension on ACE-I on and off was admitted with abdominal pain, nausea, and vomiting for 4 days. The patient took six 500 mg tablets of acetaminophen over 3 days' duration. In addition, he took enalapril 40 mg for his ill health. The patient gave a history of chronic alcohol abuse. Positive physical findings on admission include hypotension, which subsequently improved, conjunctival icterus, and tenderness over the right hypochondrium. Laboratory data showed creatinine 1.9, total bilirubin 5.7, direct bilirubin 2.7, AST 11,736, ALT 20, PT/INR 26.0/4.6, and alkaline phosphatase 141. Liver profile was repeated to check for error. Electrocardiogram showed normal sinus rhythm with left axis deviation. Abdominal sonogram showed distended gallbladder with moderate sludge, pericholecystic fluid. Acetaminophen level was 8.8. Differential diagnosis on admission included acetaminophen toxicity, shock liver, enalapril-related liver toxicity, alcoholic hepatitis, infectious hepatitis, autoimmune hepatitis, Wilson disease, and acute cholecystitis. The patient was started on intravenous *N*-acetylcysteine and vitamin K and was managed in intensive care with a plan for possible liver transplant. ANA; hepatitis A, B, C, D, and E; α_1-antitrypsin; ceruloplasmin; antimitochondrial Ab; and anti–smooth muscle Ab were negative. During the hospital course, the patient showed recovery in both symptoms and liver function tests. Isolated AST elevation noted for 24 hours and later ALT showed an increase followed by recovery of both AST and ALT. INR also improved. **Discussion:** A high index of suspicion of acetaminophen toxicity, even in low doses, is needed in patients with chronic alcohol abuse. The role of *N*-acetylcysteine is crucial in such patients and may be beneficial if the etiology of acute hepatic failure is unclear while investigations are being done. Isolated AST elevation was also an uncommon presentation in this patient.

95

WHAT IS THE MECHANISM OF ENDOTHELIN 1'S EFFECT ON ISCHEMIC VENTRICULAR TACHYCARDIA? D. Xing, J.B. Martins, University of Iowa College of Medicine and VAMC, Iowa City, IA.

Background: Endothelin (ET), one of the most potent vasoconstrictors, is known to influence ventricular tachycardia (VT). The mechanism thought to be involved includes triggered activity (TA). We investigated effects of ET-1 and the ET-1A receptor blocker BQ123 in a canine model of focal and reentrant VT in a combined in vivo and in vitro study to test the hypothesis that focal VT and TA were selectively affected. **Methods:** Thirty-eight alpha-chloralose-anesthetized dogs with 1 to 3 hours of coronary artery occlusion were studied. Three-dimensional activation mapping identified the mechanism of VT. If VT was not inducible at baseline, incremental doses of ET-1 were given until the VT was induced. If VT was reproducibly induced at baseline, BQ123 was given (2.5 μg/kg, IV), and then induction was repeated. The effect of these agents on action potentials (APs), delayed and early afterdepolarizations (DADs and EADs), and TA measured from ischemic endocardium were studied in vitro by standard microelectrode techniques. **Results:** Of 15 dogs with no VT inducible, ET-1 (0.2 μg/kg, IV) produced sustained VT of mixed reentrant and focal origin in five dogs ($p < .05$ [*] vs saline alone). ET-1 did not change effective refractory period (ERP), pacing threshold, mean arterial pressure (MAP), or infarct size (37 ± 3% [SEM] to 39 ± 4%). Of 12 dogs with reproducible reentrant VT in control, only 1 had no VT inducible after saline. Of 11 dogs given BQ123, reentrant VT was prevented in 4 of 6*; surface ECG and intracardiac T-wave alternans was blocked in all experiments. Zero of five dogs with focal origin of VT was prevented. BQ123 did not change ERP, threshold, MAP, or infarct size. In vitro APs were not substantially changed by ET-1 until rapid pacing produced AP alternans facilitated by ET-1 in 8 of 15 tissues; however, ET-1 (10-10-10-8 M) did not facilitate EADs, DADs, or TA. **Conclusion:** ET-1 promotes focal and reentrant VT under conditions of myocardial ischemia; however, in vitro tissues do not show TA as we expected. The specific ET-1A receptor blocker BQ123 significantly blocked only reentrant VT. Endothelin plays a major role in reentrant VTs in the dog model of myocardial ischemia probably by promoting AP alternans.

96

DYAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING PHARMACODYNAMIC STUDY OF SORAFENIB IN METASTATIC RENAL CELL CARCINOMA: PRELIMINARY RESULTS OF A RANDOMIZED, PHASE II TRIAL. C. Yang, O. Hahn, M. Medved, G. Karczmar, E. Kistner, T. Karrison, B. Manchen, M. Mitchell, M. Ratain, W.M. Stadler, University of Chicago, Chicago, IL.

Background: Sorafenib is an oral antiangiogenic agent with activity in renal cell cancer (RCC). We conducted a randomized, placebo-controlled trial to investigate if dynamic contrast-enhanced MRI (DCE-MRI) is a pharmacodynamic (PD) marker for sorafenib. **Method:** Patients were randomized in a double-blind manner to placebo, 200 mg bid sorafenib, or 400 mg bid sorafenib. DCE-MRI was performed at baseline and after 28 days of therapy, at which time placebo patients were rerandomized to low- or standard-dose sorafenib. RECIST-based progression was determined by CT scans performed every 12 weeks. DCE-MRI parameters, including the area under the contrast concentration versus time curve for 90 seconds after contrast injection (IAUC90), were calculated for a tumor region of interest in a blinded manner. Plasma steady-state sorafenib concentrations were obtained on day 28. **Results:** To date, 43 of a planned 66 patients have been enrolled, and 34 have undergone two protocol-defined MRIs, of which 33 are technically evaluable for the study end points. All analyses were conducted using the log ratio of the mean IAUC90 at 4 weeks versus the mean at baseline. The estimates of the log ratio and the corresponding standard deviations in the placebo, 200 mg, and 400 mg cohorts were 0.032 (± 0.235), −0.066 (± 0.138), and −0.281 (± 0.430), respectively ($p = .0156$ for linear trend between dose and the log ratio of IAUC90). These correspond to relative changes of +3%, −6%, and −24% in the placebo, 200 mg, and 400 mg cohorts, respectively. In the 27 patients with available plasma sorafenib levels, change in IAUC90 did not correlate with sorafenib steady-state levels ($p = .7507$). Current median follow-up is 20 weeks. Using a Cox proportional hazards model, IAUC90 change is not a significant predictor of progression-free survival ($p = .229$). The mean arterial pressure increased with sorafenib dose, but no correlation with IAUC90 change was detected ($p = .445$). **Conclusions:** DCE-MRI is a PD marker for sorafenib, and intrapatient variability is similar to previous reports, but the magnitude of effect in this prospective blinded study is less than previously reported. Ongoing analyses seek to assess the value of other DCE-MRI markers, such as Ktrans, and to correlate the DCE-MRI markers with more mature clinical follow-up data.

97

SYNERGISTIC ENHANCEMENT OF BREAST CANCER CHEMOTHERAPY BY PAR1 PEPDUCINS. E.J. Yang, A. Agarwal, N. Nguyen, A. Kuliopulos, L. Covic, Tufts University, Boston, MA.

Protease-activated receptor 1 (PAR1) belongs to a unique family of G protein–coupled receptors that carry their own tethered ligand at the extracellular domain. Upon proteolytic cleavage, the ligand is exposed and is allowed to intramolecularly self-activate, triggering a cascade of signaling events leading to changes in cell shape, proliferation, migration, secretion, adhesion, and gene transcription. PAR1 is identified as an oncogene, and its expression is implicated in the development and metastasis of cancers of the breast, ovary, prostate, lung, pancreas, colon, and skin. The level of PAR1 expression correlates