cardial ischemia during sexual activity than nitrates alone (-45±11% vs –18±7%, p<0.04). In conclusion patients with cardiovascular disease receiving chronic nitrate therapy may be safely switched to Trimetazidine in case of need of therapy for ED. The association between Sildenafil and Trimetazidine is more effective than nitrate therapy in the control of ischemic episodes during sexual activity.

1023-95 Excessive Bleeding With Aspirin, Clopidogrel, and Warfarin "Triple Therapy"

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Background: Numerous medical conditions require patients to receive chronic antithrombin therapy. Recent guidelines support longer and more aggressive antiplatelet therapy after myocardial infarction (MI) and following drug-eluting stent implantation or intravascular radiation. Currently, there is no safety data supporting or warning against the use of "triple therapy" with aspirin, clopidogrel and warfarin and practice patterns vary. Our aim was to estimate the risk and severity of bleeding complications in patients receiving "triple therapy". **Methods:** Via electronic medical records search, 110 patients either discharged on or receiving >2 consecutive days of "triple therapy" while hospitalized were identified and data collected regarding baseline demographics and laboratory values, indication for therapy and bleeding complications. Comparisons were made between those with and without bleeding and to historical controls. **Results:** The overall population was representative of those requiring antiplatelet and/or antithrombin therapy; mean age 68±12, 63% male; 47% prior MI; 19% prior stroke. Indication for warfarin: 35% atrial fibrillation; 35% apical thrombus/low ejection fraction. Indication for antiplatelet therapy: 70% PCI; 20% acute coronary syndrome. Bleeding occurred in 25 (23%) of patients; 14% TIMI major; 9% TIMI minor; 6% gastrointestinal; 1% intracranial; median time to major bleeding: 7 (5, 18) days. Patients who bled were more likely to be female, nonsmokers, have renal insufficiency and a prior stroke. No differences were noted in indication for therapy, aspirin dose, baseline labs or peak INR between those with and without bleeding (mean INR at time of bleed; 1.8±1.3). **Conclusion:** This is the first and only known estimate of the clinical bleeding risk on "triple therapy" with aspirin, clopidogrel and warfarin. There appears to be a significantly greater and excessive overall and TIMI major bleeding risk compared to historical controls with mono- or dual therapy (23% vs 1-10% and 14% vs 1-4%, respectively, p<0.0001). This was independent of aspirin dose and INR level. Confirmation is warranted as the implications are vast.

1023-96 A Randomized Double-Blind Placebo-Controlled Phase 2 Study on the Efficacy and Safety of Fasudil in Patients With Stable Angina

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Background: Fasudil, an orally available rho-kinase inhibitor, selectively inhibits coronary arterial vasoconstriction without affecting systemic hemodynamics. Therapeutic doses in patients with stable angina have not been previously determined.
Methods: In a phase II, multicenter, double-blind, placebo-controlled randomized trial, we evaluated the effects of fasudil on total exercise duration and time to onset of myocardial ischemia (≥ 1 mm ST-segment change) in patients with stable angina. Anti-anginal medications were limited to nitroglycerin prn and monotherapy with either a beta- or calcium-channel blocker. Cardiovascular medications including aspirin, statins, and ACE inhibitors were allowed. Patients of either sex were required to have objective evidence of myocardial ischemia, reproducible baseline exercise test times, and exercise-induced ST segment depression ≥ 1 mm. A total of 84 of the 206 patients screened met entry criteria and were randomized 1:1 to placebo or fasudil for efficacy analysis. After a 3-week washout period, fasudil or matching placebo were force-titrated from 20 mg tid to 80 mg tid with 20 mg tid increments every 2 weeks. Efficacy was evaluated by symptom-limited exercise testing after eight weeks of therapy.
Results: Exercise duration at 8 weeks was increased by 1.43 min (86.1 seconds) in the placebo group, and by 1.97 min (118.4 seconds) in the fasudil group (both p<0.001 vs baseline and p=ns to each group). Time to onset of myocardial ischemia was increased by 2.83 min in the fasudil group compared to placebo at 8 weeks (p=0.012). Heart rate and blood pressure were unchanged in both groups. A 10% discontinuation rate due to adverse events was evenly divided between the two groups.
Conclusions: This dose-finding trial demonstrated that titrating fasudil to 80 mg tid improves exercise time and time to exercise-induced myocardial ischemia in stable angina patients, and is well tolerated.

POSTER SESSION

1041

Myocardial Contraction

Sunday, March 07, 2004, 3:00 p.m.-5:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 3:00 p.m.-4:00 p.m.

1041-89 Oxygen Free Radical Damage to Essential Components of the Oxidative Phosphorylation Pathway

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Background: Stunned myocardium is characterized by impaired contractile function, and oxygen free radicals (OFR) are known to contribute to the pathogenesis. Oxidative phosphorylation is maintained in stunning, but abnormal phosphate / oxygen (P/O) ratios suggest limited uncoupling of electron transport. Recent studies have shown mitochondria are particularly sensitive to damage resulting from ischemia / reperfusion injury.
Methods: Left ventricular (LV) samples were taken from rabbit hearts after 75 min normal perfusion (control; n=6) or 15 min low flow (1 ml/min) ischemia followed by 60 min reperfusion (stunned; n=6). A third group underwent 15I/60R with the hydroxyl radical scavenger, N-(2-mercaptopropionyl) glycine (3 mM) added to the perfusate (15I/60R+MPG; n=6). Isovolumic LV pressure was measured throughout. Whole cell protein profiles were generated by two-dimensional gel electrophoresis and image analysis used to identify differentially expressed proteins, with mass spectrometry to identify proteins and define modifications.
Results: Rate pressure product at the end of the protocol was impaired in 15I/60R (61+6% baseline) in comparison to control (90±6%, mean ± SEM; p>1.5-fold difference in visible abundance). 42 proteins were shown to be modified in 15I/60R samples, 15 of which were functionally associated with redox metabolism, including 5 NADH ubiquinone oxidoreductase subunits, cytochrome c reductase and oxidase and two ATP synthase subunits. Treatment with MPG reversed the majority (n=13/15) of the observed modifications, but not that seen for NADH Uq 27kDa.
Discussion: Ischemia / reperfusion is associated with multiple alterations to mitochondrial electron transport system proteins and the ATP proton pump, which are prevented by treatment with MPG. The change to NADH Uq 27kDa was not as pronounced following the addition of MPG suggesting a two stage insult to this subunit occurring in both the ischemic and reperfusion periods. These data demonstrate another mechanism by which OFR contribute to dysfunction of reperfused myocardium.

1041-90 Opening of the Mitochondrial Potassium Adenosine Triphosphate Channel Improves Postanoxic Recovery of Conduction and Excitation-Contraction Coupling in the Developing Heart

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Background: Activation of the mitochondrial KATP (mitoKATP) channel is thought to precondition the adult heart via ROS production. To what extent modulation of mitoKATP channel alter oxidative stress and activity of the hypoxic-reoxygenated developing heart is not known.
Methods: Spontaneously beating hearts were dissected from 4-day-old chick embryos, mounted in vitro and submitted to 45 min normoxia (21% O2), 30 min anoxia (0% O2) and 60 min reoxygenation (21% O2) at 37°C. The time-course of ROS production in the ventricle was determined by measuring changes in fluorescence resulting from oxidation of the intracellular probe DCFH (10 µM) and expressed as arbitrary units per second (a.u./s). Involvement of the mitoKATP channel in oxidative stress was assessed by using the opener diazoxide (DIAZO, 50µM) or the blocker 5-hydroxydecanoate (5-HD, 500 µM). The nonselective KATP channel blocker Glibenclamide (Glib, 1µM) was also tested. Electrocardiogram and atrial and ventricular contractions were continuously recorded during experiments. Reoxygenation-induced chrono-, dromo- and inotropic disturbances, arrhythmias and alterations of electromechanical delay (EMD) in atrium and ventricle were systematically investigated.
Results: Under normoxia, heart rate (169 ± 24 bpm), PR interval (128 ± 20 ms), ventricular shortening velocity (1.9 ± 1.3 mm/s), atrial EMD (14 ± 3 ms) and ventricular EMD (9 ± 2 ms) (mean ± SD, n= 6) were similar in all groups. ROS production in control hearts was 0.18 ± 0.06 under normoxia and peaked at 1.02 ± 0.37 a.u./s (n= 6) after 10 min of reoxygenation. With respect to control, DIAZO, 5-HD, DIAZO+5-HD or Glib altered neither ROS production nor functional parameters under steady normoxia. During reoxygenation, 5-HD alone or Glib had no effect, while DIAZO doubled the burst of free radicals and increased the rate of recovery of PR interval and ventricular EMD. This DIAZO-induced protection was abolished by 5-HD.
Conclusion: In the developing heart, unlike in adult, it appears that pharmacological activation of the mitoKATP channel is prooxidant and improves atrio-ventricular conduction and ventricular excitation-contraction coupling specially during reoxygenation.