Effects of Nitroglycerin on Erythrocyte Rheology and Oxygen Unloading: Microvascular Mechanisms in Relieving Myocardial Ischemia

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Purpose: We hypothesized that myocardial blood flow (MBF) is enhanced to ischemic tissue by the direct effect of nitroglycerin (NTG) on erythrocyte rheology and that anti-ischemic effects of NTG are also afforded by its direct effects on O2 unloading.

Methods: Twelve dogs were studied at rest and during direct intracoronary infusion of NTG (0.3-3.0 μg kg⁻¹ min⁻¹). All dogs had a resting-flow reducing single-vessel stenosis. Half the dogs also had total occlusion of the remote coronary artery to remove any collateral effects. Hemodynamics, MBF, WB oxygen unloading, erythrocyte charge (EC) and electokinetics, myocardial metabolic (EM), regional myocardial O2 delivery and consumption as well as tissue O2 pressure (PO2) were determined. As compared to baseline, no changes in hemodynamics were seen during intracoronary NTG. MBF increased significantly in the central 25% of the myocardium supplied by stenosis, which was associated with an approximately 19% decrease in WbO2. There was a good correlation (r=0.87) between the two. The decrease in WbO2 was caused by a decrease in EC and an increase in EM (r=0.83). As compared to baseline, the % increase in tissue PO2 was significantly greater during NTG than the % increase in MBF, indicating enhanced O2 unloading.

Conclusions: NTG directly affects microcirculatory erythrocyte rheology that is associated with an increase in MBF in the center of the ischemic bed. It also directly enhances O2 unloading to the ischemic myocardium. Thus, direct microvascular affects of NTG also contribute to its anti-ischemic properties.

Anti-Inflammatory Effects of the V-Procteget AGT-1067 in the Canadian Antioxidant Restenosis Trial (CART-1)

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AGT-1067, the mono-succinic acid ester of probucol, is a lipophilic vascular protectant that reduces the expression of VCAM-1 and MCP-1 and has strong antioxidant properties that equipotent to probucol. We have shown in CART-1 that AGT-1067 has favorable effects on restenosis and the atherosclerotic non-PCI (reference) segments (Circulation 2003;107:552-8). The objective of the present study was to determine the effects of AGT-1067 on markers of inflammation. Prior to PCI, 305 pts were randomly assigned to 1 of 5 treatment groups: placebo (n=61), probucol 500 mg (n=60), AGT-1067 70 mg (n=60), AGT-1067 140 mg (n=64), or 280 mg (n=61) QD. Pts were treated for 2 wks prior to and for 4 wks after PCI. Fibrinogen plasma levels and circulating white blood cell (WBC) counts were measured at baseline and at the end of the 6-wk dosing period. Results: Plasma levels of fibrinogen baseline were 3.73±1.29 in the placebo group, 3.70±0.81 in the probucol group, and 3.63±1.13, 3.78±0.81 and 3.70±0.83 g/L in the AGT-1067 70, 140 and 280 mg groups respectively (p<NS). After 6 wks of treatment, fibrinogen levels were 3.56±0.76 in the placebo group, 3.63±1.05 in the probucol group, and 3.37±1.17, 3.17±0.65 and 3.21±1.01 g/L in the AGT-1067 70, 140 and 280 mg groups respectively (p<0.05 for AGT-1067 140 mg vs placebo; p<0.007 for AGT-1067 280 mg vs placebo; p=0.005 for AGT-1067 140 mg vs probucol; p=0.017 for AGT-1067 280 mg vs probucol). WBC counts decreased from baseline to end of treatment by 0.51±1.31 in the placebo group, 0.49±0.26, 0.98±1.40 and 1.09±1.26 in the AGT-1067 70, 140 and 280 mg groups respectively (p=0.025 for AGT-1067 280 mg vs placebo; p=NS for placebo vs probucol). Fibrinogen levels after 6 wks of treatment correlated inversely (p<0.07) with the previously described favorable effect induced by AGT-1067 in atherosclerotic reference segments as assessed by intravascular ultrasound. Conclusion: The vascular protectant/antioxidant AGT-1067 has anti-inflammatory effects in patients with atherosclerosis. The CART2 and ARISSE (Agressive Reduction of Inflammation Stops Events) trials are testing the anti-inflammatory hypothesis with AGT-1067.
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 ED. The association between Slidenafil and Trimetazidine is more effective than nitrate therapy in the control of ischemic episodes during sexual activity.

1025-05
Excessive Bleeding With Aspirin, Clopidogrel, and Warfarin “Triple Therapy”
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Background: Numerous medical conditions require patients to receive chronic anti-thrombin 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 or on 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 65 ± 12 yr, 63% male; 42% 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, non-smokers, 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.

1039-06
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 coro-nary 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 pr 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. Results: The mean ± SD fasudil dose 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.

1041-05
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 phos-phorylation is maintained in stunning, but abnormal phosphate / oxygen (Pi/O) ratios sug-gest 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 nor-mal perfusion (control; n=4) or 15 min low flow (1 ml/min) ischemia followed by 60 min reperfusion (stunned; n=6). A third group underwent 15/60R with the hydroxyl radical scavenger, N-(2-mercaptopropionyl)glycine (3 mM) added to the perfusate (15/ 60R+MPG; n=6). Lsovolumic 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 15/60R (61±46% baseline) in comparison to control (90±6%, mean ± SEM; p=0.5-fold difference in visible abundance). 42 proteins were shown to be modified in 15/60R 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 modifica-tions, 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 follow-ing 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.

1041-06
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 pre-condition the adult heart via ROS production. To what extent modulation of mitoKATP channel after 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). The negative selective 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 electrolymecanic detail (EMD) in atrium and ventricle were systematically investigated.

Results: Under normoxia, heart rate (169 ± 24 bpm), PR interval (128 ± 20 ms), ventricu-lar 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 reoxygen-ation. With respect to control, DIAZO, 5-HD, DIAZO+5-HD or Glib altered neither ROS production nor functional parameters under steady normoxia. During reoxygena-tion, 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-in-duced protection was abolished by 5-HD.

Conclusion: In the developing heart, unlike in adult, it appears that pharmacological acti-vation of the mitoKATP channel is present and improves atrio-ventricular conduction and ventricular excitation-contraction coupling specially during reoxygenation.