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Featured Oral Session...Treatment of Acute Myocardial Infarction

Wednesday, March 10, 2004, 10:30 a.m.-Noon

Morial Convention Center, Room 355

10:45 a.m.

The Association of Race With Angiographic and Clinical Outcomes Following Fibrinolytic Administration

Pedro Martinezclark, Dimitri Kampalamios, Sabrina A. Murphy, Stephen D. Wiviott, Brian Bigelow, Ioanna Kostis, Allen Chang, Christopher P. Cannon, Robert P. Giugliano, C. Michael Gibson, Beth Israel Deaconess Medical Center, Boston, MA, TIMI Data Coordinating Center, Boston, MA

Background: The association of race with angiographic and clinical outcomes following fibrinolytic administration is unclear. Objectives and Methods: To assess whether there are racial differences in response to fibrinolytic administration in the treatment of acute myocardial infarction. A total of 17,663 patients (16,966 Caucasians and 1,297 non-Caucasians) from the TIMI 4, 10A, 10B, and 14 and INTIME-2 trials were analyzed. TIMI flow grade, TIMI thrombus count (TTCF), TIMI myocardial perfusion grade (TMPG), and electrocardiographic (ECG) data were available in 2,296 patients. Results: Baseline comorbidities were increased among non-Caucasians including the incidence of hypertension (p<0.001), diabetes (p<0.001), active cigarette smoking (p=0.006) and a longer time to treatment (p<0.001). Angiographic outcomes did not differ by race when stratified by use of low dose fibrinolysis combined with full dose platelet glycoprotein IIb/IIIa receptor inhibition. Mortality was significantly lower among African-American patients vs. others (2.64% vs. 4.45%, p=0.012), even when adjusting for age, gender, systolic blood pressure, pulse, history of hypertension, diabetes, or CHF, prior MI, Killip class on admission, smoking, anterior MI location, and time to treatment (O.R. 0.34, 95% CI 0.12-0.92, p=0.034). Recurrent MI trended lower in African-American patients (3.0% vs. 5.0%, p=0.15). The composite of death or recurrent MI was significantly lower in African-American patients (5.3% vs. 10.6%, p=0.005) as was CHF (3.8% vs. 10.25%, p=0.001). However, when region of the patients’ enrollment (North American, Latin American, Eastern Europe, Western Europe) was added to the model, the odds ratio for neither death nor the composite of death/MI remained significant. There was no difference in the incidence of ICH or major bleeding complications. Conclusion: After adjustment for baseline characteristics and geographic region of enrollment, race was not independently associated with clinical outcomes.

11:00 a.m.

Effects of Fish Oil Supplements on Human Myocardial Omega-3 Fatty Acid Levels and Correlations With Erythrocytes

Scott A. Sands, Hakim Ali, Philip Mann, Anthony Magalski, Tracy L. Stevens, William S. Harris, Mid America Heart Institute, Kansas City, MO, University of Missouri-Kansas City, Kansas City, MO

Background: Omega-3 fatty acids (FA) have beneficial effects on the cardiovascular system and are now recommended by the American Heart Association (AHA). Their primary effect appears to be a reduction in risk for sudden cardiac death. Cell culture and animal experiments suggest that once incorporated into the myocardium, omega-3 FA (espe-cially eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) increase the resistance of the heart to ventricular fibrillation, apparently by altering the dynamics of sodium and calcium channel function. However, whether the omega-3 FA tissue levels achieved in these in vitro experiments was physiologically meaningful or not is unknown. The pur-pose of this study was to determine the effects of supplementation with omega-3 FA in humans, who did not receive thrombolytics who had higher PCI mortality, perhaps due to an increased rate of occluded infarct-related artery prior to PCI. Further studies are needed to evaluate the benefit of combined thrombolytic therapy and transfer PCI in the setting of STEMI.

Results: Supplementation raised the EPA+DHA content of the heart by 73% and of the RBC by 88% (p<0.001 for both). The increases differed for these two FA, however. In the heart, the EPA content increased by 1.6±0.6% (from 0.6±0.6% to 0.6±0.6% total FA) and in the RBC by 2.6±1.2% (from 0.4% to 1.5%). For DHA, the increases were 54% in the heart (from 1.5% to 2.3%) and 78% in the RBC (from 4.2% to 7.8%). Conclusion: These findings indicate that AHA-recommended intakes of omega-3 FA significantly increase human myocardial EPA+DHA content, and that these changes may be tracked by measurement of EPA+DHA. The myocardial omega-3 FA levels observed here may be used as physiologically-relevant benchmarks for future in vivo and in vitro experiments to explore the cellular mechanisms responsible for the cardioprotective effects of omega-3 FA.

Conclusion

Myocardial Ischemia-Reperfusion Injury Is Dependent on Lectin Complement Activation

Mary C. Walsh, Todd Bouvier, Kazue Takahashi, Lei Shi, Alan Ezekowitz, Gregory L. Stahl, Brigham and Women’s Hospital, Boston, MA, Massachusetts General Hospital, Boston, MA

Background: Complement C5 activation mediates myocardial injury following myocardial ischemia-reperfusion (MI/R). Complement activation is thought to result from natural antibodies binding to neo-epitopes on injured cells, resulting in classical pathway activation and PMN infiltration. Therefore, we evaluated the contribution of the lectin and classical pathway in MI/R injury using MBL-null (MBL-A/KCO), C1q-deficient (C1qKO), C2- and factor B-deficient (C2/Bf) or wild-type (WT) mice.

Methods: The LAD of each experimental animal was reversibly ligated for 30 min, fol-lowed by 4 h of reperfusion. After the LAD was reperfused, healthy tissue was excised and area at risk myocardium. Hearts were then stained for infarction and C3 or C1q depo-sition. Myocardial infarction (MI) is expressed as a percentage of the area at risk (infarc-tion/area at risk x 100).

Results: MI/R induced significantly larger MI in WT, compared to C2/Bf mice (33±2 vs. 12±2%, respectively; p<0.05). Addition of human C2 to C2/Bf significantly increased MI to 43±9%, comparable to WT mice and demonstrating that MI/R injury is mediated via classical and/or lectin pathway activation. WT or C1qKO mice undergoing MIR demonstr-ated myocardial C3 deposition, whereas C1qKO mice did not. Following MI/R, C1qKO mice demonstrated a MI of 47±7%, and anti-C5 mAb treatment significantly (p<0.05) reduced the infarct to 12±4%. Additionally, MBL null mice demonstrated significantly increased MI (42±4% vs. 14±6%, p=0.005) in comparison with WT mice following experi-mental MI/R. However, addition of recombinant MBL to MBL null mice significantly increased MI to 25±8%.

Conclusions: Collectively, these data demonstrate that complement activation con-tributes to MI/R injury. The complement system is not activated during MI/R by a C1q depend-ent mechanism, yet C1q is deposited. Importantly, MBL null mice demonstrate little to no infarct following experimental MI/R, yet injury is re-established upon addition of MBL. Ultimately, these findings demonstrate the therapeutic potential of lectin complement pathway blockade in MI/R and ischemic heart disease.

Cardioprotective Effects of Rosiglitazone Against Ischemia-Reperfusion Injury Are Associated With Modulation of Angiotensin Receptor Expression and Signaling

Behzad Molavi, Jawaher L. Mehta, University of Arkansas for Medical Sciences, Little Rock, AR, Central Arkansas Veterans Healthcare System, Little Rock, AR

Background: Myocardial ischemia-reperfusion injury is associated with the upregulation of renin-angiotensin system, which accentuates ischemia-reperfusion injury. The PPAR-γ ligand rosiglitazone has been shown to exert anti-inflammatory and cardioprotective effects during ischemia-reperfusion. We hypothesized that the cardioprotection by rosiglitazone is associated with alterations in angiotensin II (Ang II) receptor expression.

Methods: Male SD rats were fed either a rosiglitazone-rich diet (3mg/kg/d) or regular rat chow (control diet group) and subjected to ischemia-reperfusion (n=9 each group). A third group of rats was fed regular chow and subjected to thoracotomy and left coronary iso-la-tion to induce ischemia-reperfusion. At the end of the study, hearts were harvested for in vitro size determination as well as immunohistochemistry and Ang II AT1 and AT2 receptor mRNA determination by real-time reverse transcription polymerase chain reaction (RT-PCR). The expression of mitogen-activated protein kinase (P44/42 MAPK) and protein kinase B/Akt was assessed by Western blotting.

Results: The cardioprotective effects of rosiglitazone were confirmed by 58% reduction in infarct size (P<0.05) and preservation of myocardial contractility (decline in e dp/dt 75% less in the rosiglitazone-rich diet group) during reperfusion (P<0.005). Importantly, Ang II AT2 receptor mRNA expression was markedly (<100-fold) increased in the hearts from the rats on rosiglitazone-rich diet as compared to those on the control-diet (P<0.005). The Ang II AT1 receptor expression, which was increased in the control-diet group subjected, was suppressed (8-fold) by rosiglitazone treatment (P<0.005). P44/42 MAPK and protein kinase B/Akt were assessed by Western blotting.

Conclusion

11:15 a.m.

11:30 a.m.

ORAL CONTRIBUTIONS

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ABSTRACTS - Myocardial Ischemia and Infarction

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