POSTER SESSION

1215 Contrast Echocardiography Bioeffects, Outcomes, and Use in Evaluating Noncardiac Diseases

Tuesday, April 01, 2003, 3:00 p.m.-5:00 p.m.
McCormick Place, Hall A
Presentation Hour: 4:00 p.m.-5:00 p.m.

1215-27 Albumin and Phospholipid-Microbubbles Influence the Respiratory Burst Activity of Polymorphonuclear Neutrophil Granulocytes: An In Vitro Experiment

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Backround: Activated leucocytes can bind and subsequently phagocytose microbubbles that are used for contrast-enhanced ultrasound assessment. The purpose of this study was to investigate whether left heart contrast agents can influence the inflammatory response of human polymorphonuclear neutrophil granulocytes (PMN).
Methods: PMN isolated from peripheral blood of healthy volunteers were incubated with albumin- or phospholipid-microbubbles for 20 to 40 minutes and then stimulated with the bacterial peptide fMLP or with the calcium ionophore A23187. In other experiments activation of PMN was performed using TNF-α or the protein kinase C activator PMA before incubation with the microbubbles. The neutrophil respiratory burst activity was quantified photometrically through the superoxide-induced reduction of cytochrome C and elastase release was quantified through measuring enzymatic hydrolysis after addition of a substrate solution.
Results: Albumin- and phospholipid-microbubbles (starting at contrast agent concentrations of $5x10^4$ microbubbles/ml) induced an extensive oxidative response of human PMN to fMLP as well as to the calcium ionophor A23187 (maximum 213±34 % for albumin- and 161±17 % for phospholipid-microbubbles for fMLP and 232±23 % for albumin- and 169±23 % for phospholipid-microbubbles for A23187). Activation of PMN with TNF-α or with PMA induced also an extensive oxidative response of human PMN which was in the case of TNF-α possible at 10–fold lower contrast agent concentrations. The effect of both contrast agents on burst activity could be significantly impaired through preincubation of the cells with the polymerisation-inhibitor Cytochalasin B, indicating that phagocytosis of the microbubbles contributes to their effect on the burst activity. Albumin-microbubbles could also significantly amplify the release of neutrophil elastase after stimulation of PMN with fMLP or PMA.
Conclusions: Left heart contrast agents used for contrast-enhanced ultrasound assessment can activate human PMN inducing an extensive respiratory burst to secondary stimuli. The potential clinical relevance of this effect remains to be elucidated.

1215-28 Myocardial Capillary Damage in Myocardial Contrast Echocardiography: Influence of Ultrasound Transmit Energy

Peng Li, Luqin Cao, Chunyan Dou, William F. Armstrong, Douglas Miller, University of Michigan, Ann Arbor, MI

Background: Previous animal work has demonstrated both PVCs and evidence of capillary leakage after intravenous contrast injection for MCE.
Purpose: To evaluate the frequency of PVCs and extent of capillary damage during MCE as a function of ultrasound transmit energy.
Methods: 22 anesthetized rats with a tail vein catheter for contrast injection were imaged during continuous ECG recording in a 37°C water bath using 1:4 triggered fundamental imaging at end-systole at 4 ultrasound transmit energy settings, 0dB(measured equivalent Mechanical Index, MIeq=1.5), -3dB(MIeq=1.1), -6dB(MIeq=0.8) and –12dB(MIeq=0.4). A short axis view of left ventricle was obtained with a phased array scanhead (1.7MHz, GE System Five). Evans blue dye was injected as a marker for microvascular leakage. Optison™ (Mallinckrodt) was injected at 0.5 ml/kg followed by a 1ml saline flush. After 5 minutes of ultrasound exposure, the rats were euthanized and the hearts excised for examination.
Results: PVCs occurred in all 6 rats at 0dB, 2 of 5 rats at –3dB, 1 of 6 rats at –6dB, and none of 5 rats at –12dB. From 0dB to –12dB, the Evans blue area on the heart surface decreased: 111.6±21.5mm^2, 78.6±10.6mm^2, 61.6±6.2 mm^2, and 12.1±3.9 mm^2, p<0.001; petechial hemorrhages on the heart surface were 84±15, 53±19, 34±13, and 0±0, p<0.05. No PVCs occurred in the –12dB animals even in the presence of significant capillary leakage on the heart surface. **Conclusion:** At greater than usual diagnostic doses of Optison, MCE is associated with transmit power dependant capillary damage.

1215-29 Time Course of Microvascular Leakage Induced by Myocardial Contrast Echocardiography

Peng Li, William F. Armstrong, Douglas L. Miller, University of Michigan, Ann Arbor, MI

Background: Evidence of microvascular leakage induced during myocardial contrast echocardiography (MCE) icludes epicardial petechial hemorrhage and leakage of Evans blue dye in the myocardium and on the epicardium. The time course of microvascular leakage after acute ultrasound exposure was investigated by delaying the injection of Evans blue until after exposure.
Methods: 25 hairless rats (296.9±34.5g) were imaged in a 37°C water bath. A left ventricular short axis view was imaged for 8 minutes with a phased array scanhead operated at 1.7MHz (GE System Five). All ultrasound exposures were identical at a measured equivalent MI=1.7 (0dB, 1.9MPa), with 1:4 at end-systolic triggering. Optison™ (Mallinckrodt) was injected at 0.5 ml/kg, and Evans blue dye (100 mg/kg) was injected A) 1 minute before MCE, or B) 5 min, C) 10 min or D) 20 min after MCE. A Sham MCE group was also tested with imaging but with Optison injection after scanning had ceased. The number of visible petechia were counted in excised hearts, and compared to the area of evident Evans Blue leakage determined by image analysis of photographs of the dorsal surface of the hearts.
Results: No significant microvascular leakage occurred for sham expsosure. As expected, the petechial hemorrhage counts were indistingquishable for the (identically exposed) groups, with 210±87, 228±124, 201±81 and 193±32 petechiae for groups A through D, respectively. In contrast, the Evans blue leakage areas decreased quickly: 83.8±17.2 mm^2; 46.1±19.7 mm^2; 32.8±18.0 mm^2 and 4.7±2.1 mm^2 for group A, B, C, and D, respectively. Evans blue leakage area was statistically increased (P<0.05, ANOVA test) for groups A, B and C, but not D, relative to shams.
Conclusions: Microvascular leakage induced acutely during MCE progressively diminishes after cessation of imaging to sham values after about 20 min. The findings have implications for the safety of diagnostic MCE and for therapeutic drug/gene delivery with this technique.

1215-30 Time- and Energy-Dependent Ischemic-Like ECG Changes During Myocardial Contrast Echocardiography in Rats

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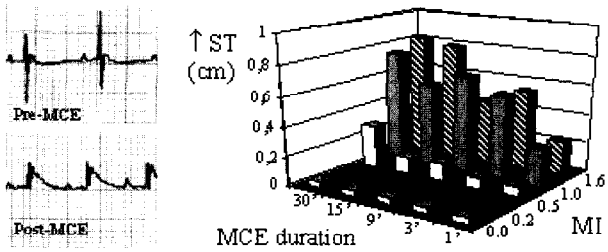
Background. Previous studies have shown that the combined exposure of rat hearts to contrast microbubbles and high mechanical index (MI) ultrasound (US) results in time- and energy-dependent myocardial alterations, which are most probably ischemic in origin. To test this hypothesis further, we investigated the occurrence of ischemic ECG changes during contrast echocardiography (MCE) in 117 anesthetized rats exposed to both PESDA and triggered (1Hz) US at MI of 0.2, 0.5, 1.0 and 1.6 for 1, 3, 9, 15 or 30 min. A 6 leads peripheral ECG was obtained just before, and immediately after MCE. ST-segment changes were measured in lead I at the J point, using the P-R interval as reference. Results. In control animals and in those exposed to US at MI of 0.2, no ST-segment changes were noted. By contrast, significant ST-segment elevation occurred in all animals exposed to an MI > 0.2 (P<0.05 vs. controls and MI:0.2). The amplitude of ST-segment elevation increased progressively with both the duration of US exposure and MI (graph). Conclusions. Our data show that exposure of rat hearts to high-MI US and PESDA induces ischemic-like ECG changes, whose severity is directly proportional to the energy applied and the duration of insonation.



1215-31 Clinical Utility of Echocontrast in Suboptimal Echocardiograms: A Multistudy Analysis

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Purpose: A 16-segment model is often used in echocardiography to evaluate myocardial function. In some echocardiographic views, an entire coronary vessel territory may be represented by a single segment. If such a segment is not visualized, single vessel disease of subtending artery may be overlooked. The correct identification of wall motion abnormalities in these segments is therefore critical for the diagnosis of CAD in these vessel territories.
Methods: We analyzed data from cardiac examinations of 138 patients enrolled in two identical studies with sulfur hexafluoride microbubbles (SonoVue, Bracco). All patients had two or more segments poorly seen on a baseline ultrasound examination. For our analysis we used a 16 segment model and defined the following segments as critical: 4 chamber view: apical septal, mid lateral, basal lateral; 2 chamber view: apical anterior, mid inferior, basal inferior. Results: In 119 out of the 138 baseline examinations at least one "critical" segment was not visualized. After injection of 2 mL of SonoVue, 84 of these patients had complete visualization in all critical segments. These results were confirmed by four independent blinded reviews (2 per study), in which the number of studies with at least one critical segment not visualized decreased after SonoVue: from 64 to 29 (Reader 1 Study A), from 69 to 33 (Reader 2 Study A), from 38 to 17 (Reader 1 Study B) and from 57 to 6 patients (Reader 2 Study B). Conclusions: The inability to visualize critical segments on standard 2- and 4- chamber apical views is a frequent cause for referral to other more invasive imaging modalities. By converting critical myocardial segments from non-diagnostic to diagnostic in 84 out of 119 patients (71%), a successful ultrasound examination was possible in over 70% of patients with clinically inconclusive baseline studies. These findings suggest that contrast echo can increase the reliability of echocardiography while potentially decreasing the cost of evaluating patients with suspected CAD.