Young Investigator's Award Competition (YIA)

Monday, June 23, 2014

2014 ARTHUR E. WEYMAN YOUNG INVESTIGATOR'S AWARD COMPETITION

Monday, June 23, 2014
Presented 8:00 am-9:30 am

Echocardiography in Arrhythmias / Atrial Function
YIA-1

Pediatric and Adult Congenital Heart Disease
YIA-2

Contrast Echocardiography and New Technology
YIA-3

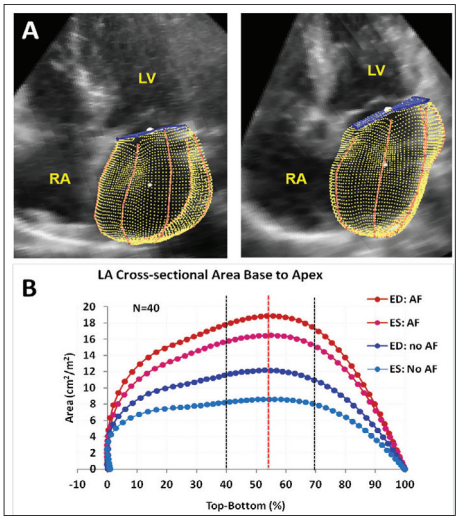
Ventricular Function / Myocardial Mechanics
YIA-4

YIA-1

Left Atrial Cross Sectional Area, a Marker of Left Atrial Shape, is a Novel Risk Factor for Cardioembolic Stroke and Recurrence of Ischemic Stroke

Timothy Tan, Octavio Pontes-Neto, Mark Handschumacher, Maria C. Nunes, Yong-Hyun Park, Victoria Piro, Yuan Jiao, Gyeong-Moon Kim, Johanna Helenius, Cashel O'Brien, Xin Zeng, Karen Furie, Hakan Ay, Judy Hung. Massachusetts General Hospital, Boston, MA

Background: Cardioembolic stroke (CE) carries significant morbidity and mortality. Left atrial (LA) size has been inconsistently associated with CE risk, due to variation in LA remodeling. Specifically, LA shapes with a larger mid cross sectional area (Fig A; i.e. more spherical) may have higher association with CE due to abnormal flow dynamics or predisposition to atrial fibrillation (AF). We hypothesized that differential LA remodeling impacts on the pathophysiologic mechanism of AF, CE stroke and recurrence. **Methods:** LA shape was quantified using the maximum LA cross sectional area (LACSA) by 3D echo. Differences in LACSA was used to characterize LA remodeling in a cohort of 40 prospectively recruited patients with ischemic stroke (IS) with AF (n=13) vs those with no AF (n=27) using customized software (Omni4D) and 3D echo. LA function (EF) was calculated from 3D LA volumes at end-diastole and end-systole and the relationship to LACSA examined. To determine if LA shape influences flow dynamics, flow velocity profiles were measured in spherical versus ellipsoidal *in vitro* models. 2D LACSA was derived from measurements from 3 planes in 2D views, validated with 3D echo, then subsequently applied in a separate cohort of 1275 IS patients who were followed up for 90 days for recurrence, along with other echocardiographic parameters. **Results:** LA shape varied between the AF and non-AF groups with LACSA from the mid portion (40-70% on plot) showing the greatest significant difference ($p<0.001$; Fig B). *In vitro* flow models showed shape related differences in mid level flow velocity profiles. LA function was worse in patients with IS and AF compared to patients without AF. 2D LACSA and LA volume (LAV) correlated well with 3D measures. In the 1275 IS patients, increased LACSA (8.6 ± 2.3 vs 6.4 ± 1.8 cm^2/m^2; $p<0.001$) and LAV (50.6 ± 18.6 vs 34.0 ± 13.8 ml/m^2; $p<0.001$) were associated with CE stroke. In those with CE strokes, 22 with recurrence had greater LA CSA (9.5 ± 2.4 vs 8.4 ± 2.3 cm^2/m^2; $p=0.04$) and LAV (58 ± 19 vs 49 ± 18 ml/m^2; $p=0.04$). Multivariable analysis adjusting for age, AF and LVEF showed that LAV (OR 1.024; $p=0.04$) and LA CSA (OR 1.218; $p=0.04$) were predictors of recurrence. **Conclusion:** LACSA is a marker of LA shape associated with AF, CE stroke and recurrence, reflecting importance of differential LA remodeling in the mechanism of CE risk.



YIA-2

Changes in Speckle-Tracking Echocardiographic Measures of Right Ventricular Function Correlate with Changes in Measures of Exercise Function after Percutaneous Implantation of the Edwards SAPIEN Transcatheter Heart Valve in the Pulmonary Position

Shahryar M. Chowdhury[1], Ziyad M. Hijazi[2], John T. Fahey[3], John F. Rhodes[4], Saibal Kar[5], Raj Makkar[5], Michael Mullen[6], Qi-Ling Cao[2], Kyle Bilhorn[7], Lazar Mandinov[7], Girish S. Shirali[8]. [1]Medical University of South Carolina, Charleston, SC; [2]Rush University Medical Center, Chicago, IL; [3]Yale-New Haven Hospital, New Haven, CT; [4]Miami Children's Hospital, Miami, FL; [5]Cedar Sinai Medical Center, Los Angeles, CA; [6]The Heart Hospital, London, United Kingdom; [7]Edwards Lifesciences, LLC, Irvine, CA; [8]Children's Mercy Hospital, Kansas City, MO

Background: Speckle-tracking echocardiographic (STE) measures of right ventricular (RV) function appear to be more sensitive than traditional measures in detecting changes in function after transcatheter pulmonary valve (TPV) implantation. Measures of exercise function, such as the V_E/V_{CO2} slope, have been shown to be prognostic of mortality in patients with repaired Tetralogy of Fallot. Our objective was to evaluate the correlation between changes in STE measures of RV function and changes in measures of exercise function after SAPIEN TPV placement. **Methods:** Echocardiograms and cardiopulmonary exercise testing were performed at baseline and 6 months after TPV placement in 24 patients from 4 centers. A single, blinded observer performed offline STE analysis of DICOM images using vendor-independent software. Speckle-tracking measures of function included peak longitudinal strain, strain rate, and early diastolic strain rate. Conventional echocardiographic measures of RV systolic and diastolic function were also assessed. Cardiopulmonary exercise testing was performed using a ramp workload protocol. Anaerobic threshold was determined by use of the modified V-slope method. Echocardiograms and exercise stress tests were interpreted by Core laboratories. **Results:** All patients demonstrated relief of significant pulmonary regurgitation, and stenosis if present, after TPV implantation. No significant changes were detected in conventional echocardiographic measures of RV function. Improvements in RV longitudinal strain ($-16.9 \pm 3.5\%$ vs. $-19.7 \pm 4.3\%$, $p < 0.01$) and strain rate ($-0.9 \pm 0.4 s^{-1}$ vs. $-1.2 \pm 0.4 s^{-1}$, $p < 0.01$) were noted. There were no changes in peak VO_2, VO_2 at anaerobic threshold (AT), or respiratory exchange ratio at AT between baseline and 6 months. In contrast, the V_E/V_{CO2} slope improved (32.4 ± 5.7 vs. 31.5 ± 8.8, $p = 0.03$). The change in V_E/V_{CO2} correlated with the change in RV longitudinal strain ($r = 0.50$, $p = 0.03$) and early diastolic strain rate ($r = 0.53$, $p = 0.02$). Changes in conventional echocardiographic measures of RV function did not correlate with changes in measures of exercise function. **Conclusion:** Improvements in RV longitudinal strain and strain rate are seen at six months post TPV, as are improvements in V_E/V_{CO2}. Changes in STE measures of RV systolic and diastolic function correlate with changes seen in V_E/V_{CO2}. STE measures of RV function appear to hold the potential for being used as predictors of improved outcomes in patients requiring TPV implantation. Future studies should directly assess the prognostic significance of STE measures of RV function in this population.

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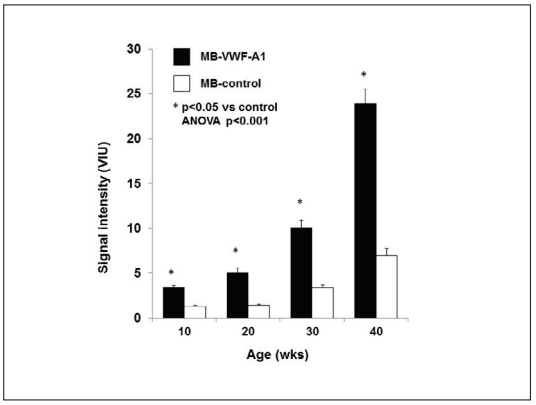
YIA-3

Platelet Attachment to Vascular Endothelium Occurs in Both Early and Late-Stage Atherosclerosis Secondary to Dysregulation of Von Willebrand Factor: Evaluation by Contrast Ultrasound Molecular Imaging

Chi Young Shim[1], Ya Ni Liu[1], Tami Atkinson[1], Mackenzie Treible[1], Aris Xie[1], Yue Qi[1], Ted Foster[1], Todd Belcik[1], Zaverio Ruggeri[2], Jose Lopez[3], Jonathan R. Lindner[1]. [1]Oregon Health & Science University, Portland, OR; [2]Scripps Research Institute, La Jolla, CA; [3]University of Washington, Portland, OR

Background: Non-thrombotic platelet-endothelial interactions may play an important role in atherosclerosis. Methods for assessing these interactions *in vivo* are lacking. Using contrast ultrasound molecular imaging (CMI), we tested the hypothesis that platelet-endothelial interactions occur both early and late in atherosclerosis. We also tested whether platelets attach to adherent leukocytes or to endothelial Von Willebrand factor (VWF) which can become activated with dysfunction of its regulatory enzyme ADAMTS-13. **Methods:** Atherosclerotic mice deficient for the LDL-receptor and Apobec-1 were studied as an age-dependent model of progressive atherosclerosis at 10, 20, 30, and 40 wks of age. In vivo CMI of the thoracic aorta was performed with microbubbles (MB) bearing: (a) VWF A1-domain peptide to image platelet GPIbα, (b) GPIbα to detect endothelial VWF; or (c) control MBs. CMI performed after platelet immunodepletion was used to assess specificity of platelet CMI. To evaluate mechanism, CMI was performed after inhibiting P-selectin or administration of exogenous ADAMTS-13. Flow chamber assessment of ex vivo aortas was used to assess VWF multimerization using targeted fluorescent nanospheres. **Results:** CMI detected platelet adhesion in the aorta which increased progressively as disease advanced from fatty streaks (10-20 wks) to complex large plaques without rupture (40 wks) (Figure). Platelet depletion completely eliminated selective enhancement for GPIbα-targeted MBs. CMI signal with VWF-targeted MBs was higher than control MBs at 10 wks of age and progressively increased with age (ANOVA p=0.017). Inhibition of P-selectin had a modest effect on platelet CMI signal (20-40% reduction); whereas ADAMTS-13 completely abolished both platelet and VWF signal. Linear aggregates of targeted nanospheres were seen on the ex vivo aortic surface confirming VWF multimers which increased with age. **Conclusion:** In early to advanced atherosclerosis, platelet attachment to the endothelium without plaque rupture can be detected in vivo by CMI. These interactions are largely due to progressive endothelial VWF multimerization which occurs with loss of ADAMTS-13 activity. These findings suggest that platelet GPIbα may be a therapeutic target for reducing platelet-endothelial interactions in atherosclerosis.



YIA-4

Mechanism of Early Diastolic Intraventricular Pressure Gradients During Exercise

Kotoko Matsui[1], Ken Takahashi[1], Noboru Tanaka[1], Maki Kobayashi[1], Katsumi Akimoto[1], Masahiko Kishiro[1], Keiichi Itatani[2], Kagami Miyaji[2], Toshiaki Shimizu[1]. [1]Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan; [2]Department of Hemodynamic Analysis, Kitasato University School of Medicine, Kanagawa, Japan

Background: During early diastole, there is a progressive intraventricular pressure gradient (IVPG) extending from the left atrium (LA) to the left ventricular apex, which plays an important role in left ventricular diastolic function. In response to exercise, the IVPG increases, allowing for rapid filling without an abnormal increase in LA pressure. Although IVPG plays an important role in exercise intolerance, the mechanism of increasing IVPG during exercise remains unclear. The aim of this study was to investigate the IVPG during exercise and the mechanism underlying the increase in the IVPG during exercise. **Methods:** Eighteen healthy men (age range, 22-33 years) underwent echocardiography at rest as well as during supine bicycle exercise (starting at 25 W, with 25-W increments every 5 minutes). Left ventricular torsion, untwisting rate, circumferential strain (CS), CS rate (CSR), and left ventricular length strain (LVLS) ratio and its rate (LVLSR) were measured using speckle-tracking and tissue Doppler imaging. Furthermore, the percentage of untwisting and lengthening of CS and LS at early systole was measured. In addition, IVPG was measured through the color Doppler M-mode using Euler equations with our own program. **Results:** The peak IVPG was observed at 121.0% ± 6.0% of systolic duration at rest, 116.7% ± 5.4% of systolic duration at 50 W, and 116.4% ± 5.4% of systolic duration at 100 W, but these values were not significantly different. Although the peak untwisting occurred close to the peak IVPG, CSR and LVLSR occurred significantly later. The average IVPG was 0.35 ± 0.08 mmHg at rest, 0.57 ± 0.13 mmHg at 50 W, and 0.67 ± 0.16 mmHg at 100 W. The lengthening of CS at early diastole and untwisting rate/LV correlated with IVPG at rest. CS and LVLSR correlated with IVPG at 50 W and 100 W. Under all workload conditions, the untwisting rate, lengthening of CS at early diastole, CSR, and LVLSR were found to be independent predictors of IVPG on multivariate analysis. **Conclusion:** The LV untwisting rate/LVL and lengthening of CS at 120% of systole correlated with IVPG at rest. However, LVLSR and CSR was also found to be associated with increased IVPG during exercise. As both peak IVPG and peak untwisting rate occurred at around 120% of systole, untwisting and lengthening of CS during early diastole might be the active mechanisms that induce the IVPG. Although CSR and LSR were associated with the IVPG, they would be consequences rather than causes of the IVPG because they occurred significantly later than the peak IVPG. These findings offer new insight into left ventricular diastolic function.