Technion
Israel Institute of Technology

University of Michigan
Cardiovascular Center

The 1st Annual D. Dan and Betty Kahn University of Michigan-Technion Collaborative Cardiovascular Research Symposium

Tuesday, October 4, 2011

University of Michigan

Cardiovascular Center

Table of Contents

Tuesday, October 4, 2011

Symposium Agenda

7:45 am	Transportation from Campus Inn to Cardiovascular Center
8:00-8:30 am	***Breakfast***
	Omer Berenfeld: Program Introduction
8:30-8:45 am	***Opening Remarks***
	Michael Aviram; Tanenbaum Chair Professor in Preventive Medicine, Chief, Lipid Research Laboratory, and Senior Vice Dean, Ruth & Bruce Rappaport Faculty of Medicine, Technion.
	David Pinsky; Ruth Professor and Chief, Cardiovascular Medicine, Director, Cardiovascular Center, Senior Scholar, Taubman Medical Research Institute, University of Michigan.
	Eliezer Shalev; Chairman of the Department of Obstetrics & Gynecology at Haemek Medical Center in Afula, Israel; Dean of the Faculty of Medicine in the Technion Institute of Technology.
8:45-12:00 pm	***Presentations***

Chair: **Uri Rosenschein**, Head, Department of Cardiology, Bnai Zion Hospital, Ruth & Bruce Rappaport Faculty of Medicine, Technion.

8:45-9:00	**Ofer Binah** (Technion): Functional Properties of Induced Pluripotent Stem Cells-Derived Cardiomyocytes in the Healthy and Diseased Myocardium.
9:00-9:15	**Jérôme Kalifa** (UM): Fibrosis in Atrial Fibrillation: Is it Reversible?
9:15-9:30	**Marcelle Machluf** (Technion): From Nano – To Micro Technology: Treating Cancer and Broken Heart.
9:30-9:45	**Ami Aronheim** (Technion): The Role of the ATF3 Transcription Factor in Mediating Cardiac Hypertrophic Signaling Pathways.
9:45-10:00	**Omer Berenfeld** (UM): Time-Course of Atrial Fibrillation Remodeling.

10:00-10:20 am ***Break***

Chair: **Omer Berenfeld,** Associate Professor of Internal Medicine, University of Michigan Medical School and Associate Professor of Biomedical Engineering, College of Engineering.

10:20-10:35	**Hakan Oral** (UM): Ablative Treatment of Atrial Fibrillation.
10:35-10:50	**Ronen Jaffe** (Technion): Strategies for Prevention of Distal Coronary Embolization and No-Reflow During Percutaneous Coronary Intervention.
10:50-11:05	**Michael Aviram** (Technion): HDL–Associated Paraoxonase 1 (PON1) Inhibits Macrophage Foam Cell Formation and Atherosclerosis Development.
11:05-11:20	**Ralph Lydic** (UM): Sedative/Hypnotic Medications Depress Breathing in Rats with Metabolic Syndrome.
11:20-11:35	**Yoram Agmon** (Technion): Novel Insights into Cardiac Function Using Echocardiographic Myocardial Deformation (Strain) Imaging.
11:35-11:50	**Theodore J. Kolias** (UM): Advances in the Echocardiographic Assessment of Cardiac Function.

12:00-1:00 pm ***Lunch***

1:00-5:00 pm ***Presentations***

Chair: **Ofer Binah,** Professor of Physiology, Department of Physiology, The Sohnis Family Stem Cells Center, Ruth & Bruce Rappaport Faculty of Medicine, Technion

1:00-1:10	**Ora Pescovitz** (UM): Executive Vice President for Medical Affairs and Professor of Pediatrics and Communicable Diseases, Medical School
1:10-1:25	**Uri Rosenschein** (Technion): Ultrasound Thrombolysis - Waves, Bubbles and Clots.
1:25-1:40	**Jordan Shavit** (UM): Identifying Modifiers of Thrombosis Using Zebra-Fish Models.
1:40-1:55	**Oliver Kripfgans** (UM): Partial Volume Processing in 4D Cardiac Doppler Flow Estimation.
1:55-2:10	**Benedict R. Lucchesi** (UM): Inhibition of the thromboxane A_2 (TxA_2) receptor and thrombin maintains vessel patency after thrombolysis with alfimeprase vs. rt-PA.
2:10-2:25	**Yoav Turgeman** (Technion): Cardiac Assessment of Hypertensive Pregnant Women.
2:25-2:40	**Jeffrey L. Platt** (UM): Structural and Functional Changes in the Immune System Caused by Cardiac Surgery in Infancy.

2:40-3:00 pm ***Break***

Chair: **Jerome Kalifa,** Assistant Professor of Internal Medicine, University of Michigan Medical School.

3:00-3:15	**David Bach** (UM): Un-operated Patients with Severe Aortic Stenosis or Mitral Regurgitation: Barriers to Appropriate Management.
3:15-3:30	**Avraham Shotan** (Technion): Acute Coronary Syndrome in Israel: Data from ACSIS Registry.
3:30-3:45	**Maureen Sartor** (UM): Bioinformatics Tool Development for High-throughput Cardiovascular Disease Research.
3:45-4:00	**John G. Younger** (UM): The Fluid Dynamics of Bloodstream Infections.
4:00-4:15	**David Ginsburg** (UM): Hemostasis in Host Defense from Microbial Pathogens.
4:15-4:30	**Senior Associate Dean Joseph Kolars** (UM): University of Michigan Global Initiatives.

4:30-4:40 pm	***Omer Berenfeld (UM): Evening Logistics***
4:45	Transportation to Campus Inn (two trips will be made)
6:00	Transportation to Biomedical Science Research Building

6:15 pm	***Reception: Biomedical Science Research Building (Invitation Only)***
7:00	Dinner
	Opening Remarks:
	Lawrence Jackier President North American Technion Society
	Dean, Eliezer Shalev Ruth & Bruce Rappaport Faculty of Medicine
	Senior Associate Dean, Joseph Kolars Education and Global Initiatives
	Kim Eagle Director, Cardiovascular Center
	Michael Aviram and David Pinsky Thank you's and "Charge for the Future"
9:00 & 9:30 pm	***Transportation to Campus Inn (two trips)***

Ofer Binah, PhD | 8:45-9:00

Molecular characterization and functional properties of induced pluripotent stem cells-derived cardiomyocytes from healthy and diseased individuals.

In view of the therapeutic potential of cardiomyocytes derived from human induced pluripotent stem cells (iPSC-CM), our overall goal is to investigate their molecular characteristics, functional properties related to the excitation-contraction coupling (e.g., $[Ca^{2+}]_i$ handling), pacemaker function and underlying ion currents, the effects of □-adrenergic stimulation, and responsiveness to common modifiers of cardiac function (e.g., I_f blocker). The iPSC clones we investigated were derived from human foreskin fibroblasts, dermal fibroblasts and hair keratinocytes. Reprogramming was accomplished by infecting the cells with retroviruses containing the four human genes: OCT4, Sox2, Klf4 and C-Myc. Our major findings show that iPSC-CM: (1) express cardiac specific RNA and proteins; (2) exhibit regular pacemaker activity; (3) exhibit key features of the excitation contraction coupling machinery; (3) respond to ryanodine and caffeine (albeit less than adult cardiomyocytes), and express the SR-Ca^{2+} handling proteins ryanodine receptor and calsequestrin. Hence, our work demonstrated that iPSC-CM exhibit features resembling the adult myocardium, and thus constitute a potential source for cardiac regeneration. Additionally, we investigated iPSC-CM generated from skin biopsies and hair obtained from patients with the inherited arrhythmia Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and LQT1. Our study focused on the autosomal recessive form of the disease caused by the missense mutation D307H in the cardiac calsequestrin gene, CASQ2. The major findings were that the CPVT cardiomyocytes demonstrated catecholamine-induced arrhythmogenesis, indicating that the CASQ2-mutated cardiomyocytes can be used to study the electrophysiological mechanisms underlying CPVT and for tailoring patient-specific anti-arrhythmic therapy.

Jérôme Kalifa, MD, PhD | 9:00-9:15

Fibrosis in Atrial Fibrillation: Is it Reversible?

In the heart, excessive fibrosis is a major factor leading to pump dysfunction and heart failure and is also a substrate for atrial and ventricular arrhythmias. These disorders affect millions of patients worldwide and therapeutic options are at times limited and marginally efficient. For instance, patients with drug-resistant arrhythmias such as atrial fibrillation might be eligible to catheter ablation procedures. Ablation is successful in targeting defined myocardial regions but is associated with an increased scar formation which may enhance cardiac remodeling and ultimately decrease efficacy. **T**ransforming **G**rowth **F**actor Beta 1 (**TGF-β_1**) is a pro-fibrotic cytokine that induces fibroblast proliferation and enhances the synthesis of extracellular matrix proteins such as collagen. Thus, TGF-β_1 represents a valuable target for therapies aiming at decreasing or reversing fibrotic progression. However, the heterogeneity of the disease process is a limitation of global anti-fibrotic strategies. Indeed, TGF-β_1 might be deleterious in specific regions of the heart, leading to wall stiffness, scar formation and arrhythmias, but is essential in other regions to enhance collagen and fibrosis formation and strengthen the extra-cellular matrix. Ideally, anti-fibrotic therapies should be targeted to regions or areas decisively causing arrhythmias or dysfunction, while other regions are spared. The ***general objective*** of the collaboration between Marcelle Machluf's laboratory at Technion and Jérôme Kalifa's laboratory at the University of Michigan is to develop and implement means of *regional in vivo delivery of* the anti-fibrotic gene that encodes for decorin, a small leucine-rich proteoglycan which negatively regulates TGF-β_1 by neutralizing its biological activity. ***Our long term plan*** is to develop therapeutic options for patients with ventricular and atrial arrhythmias in which regional interstitial fibrosis is known to play a major pathophysiological role. We envision technologies that would be alternate or adjuvant to existing cardiac arrhythmias ablation procedures.

Marcelle Machluf, PhD | 9:15-9:30

From Nano – To Micro Technology: Treating Cancer and Broken Heart.

Our laboratory is engaged in developing technologies and applied solutions to major challenges in non-viral gene therapy, cardiovascular tissue engineering and drug delivery. In the realm of gene therapy, our goal is to develop non-viral systems and technologies for DNA delivery into mammalian cells and tissue. The vision in that aspect is to advance these technologies to the point of technology transfer and implementation in clinical settings. In the last years, a system for DNA delivery was developed and studied; therapeutic ultrasound waves (TUS, patent filed). The research demonstrated for the first time, the *in-vivo* efficacy of TUS gene-delivery in cancer therapy. The research demonstrated that prostate cancer inoculated in animals could be significantly inhibited by TUS-enhanced repeated administration of DNA encoding for PEX, an anti-cancer drug. We hope to engage and modulate this technology to deliver gene that encode for anti-inflammatory factors to the injured cardiac tissue. We have also developed a new-targeted system, which is based on unique nano-vehicles produced for the first time from the membrane of stem cells. These nano-scale size vehicles have the capabilities to entrap genetic materials or drugs and can be targeted to inflammated or cancerous tissue.

In the field of tissue engineering, the laboratory has filed patents on isolating natural biological material, the ECM, which can be used in the future for engineering heart tissue and blood vessels. These materials are isolated in full thickness from porcine heart and blood vessels using a new method and protocol. These materials have been shown to have superior biocompatible-and mechanical strength, compatible to the ones that the heart and blood vessels exhibit. The long-term goal of this research is to use these materials as a patch to repair heart defects or as injectable material that solidify in-situ. The emphasis in the patch cardiac engineering area of research is to generate ECM of full thickness (12-15 mm). As generation of thicker myocardial-like tissue constructs is limited due to diffusion limitations (~100 µm), and is lacking of proper vascular network, we focus on the development of support systems which enable the cultivation of thicker constructs such as perfuse electrical and mechanical bioreactors and regenerating in-situ vascular networks.

Ami Aronheim, PhD | 9:30-9:45

The Role of the Activating Transcription Factor 3, ATF3, in Heart Hypertrophy.

The atria respond to various pathological stimuli including pressure and volume overload with remodeling and dilatation. Dilatation of the left atrium is associated with atrial fibrillation. The mechanisms involved in chamber specific hypertrophy are largely unknown.
ATF3 is an immediate early transcription factor found at the receiving end of multiple stress and growth stimuli. Cardiac specific expression of ATF3 is sufficient to results in atrial dilatation. The resulting atrial dilatation is most likely an acquired phenotype and is developmentally independent. Moreover, the atrial phenotype is reversible following abolishment of transgene expression thus may be a relevant therapeutic target for preventing atrial dilatation and atrial fibrillation.
ATF3 expression is highly elevated in response to acute angiotensin II stimulation (AngII). ATF3 expression is regulated by angiotensin-receptor-mediated signaling *in vivo* and *in vitro* at the transcriptional level. ATF3 induction is mediated by cooperation between both the AT_{1A} and AT_2 receptor subtypes and is independent of its effect on blood pressure. In contrast to adrenergic stimulation that induces ATF3 in all heart chambers, ATF3 induction in response to angII occurs primarily in the left chambers. The mitogen activated protein kinase (MAPK) signaling pathways are also activated primarily in the left chambers in response to AngII. ATF3 KO mice with chronic infusion of either AngII or phenylephrine display reduced heart/body weight ratio, lower induction of collagen type I and reduced expression of embryonic gene program. Thus ATF3 expression in the heart plays an important role in processes leading to heart hypertrophy.

Collectively, our data strongly place ATF3 as a unique nuclear protein target in response to both acute and chronic neuro-hormonal stimuli. The spatial expression of ATF3 may add to the understanding of the signaling pathways involved in cardiac response to neuro-hormonal stimulation, and in particular to the understanding of left atrial generated pathology such as cardiac hypertrophy and atrial fibrillation.

Omer Berenfeld, PhD | 9:45 – 10:00

Time-Course of Atrial Fibrillation Remodeling.

Introduction:

During paroxysmal atrial fibrillation (AF), maximal dominant frequency (DF) is higher in the left atrium (LA) than in the right atrium (RA). It has been found that DFs in patients with persistent AF are higher than those in paroxysmal AF, however, the time-course of the DFs acceleration and possible redistribution across the atria are not known. We have developed a sheep model of long-term (>3 months) tachypaced induced AF to study in-vivo characteristics of the arrhythmia remodeling. Here we test the hypothesis that atrial DFs increase gradually and predictably as the AF becomes persistent with a fixed LA to RA DF difference.

Methods:

AF was induced using continuously a fast pacing protocol that consisted of repetition of a 30 sec long episode of 20 Hz pacing and 10 sec long episode of sensing through a RA lead (N=7). Electrograms were obtained from the RA lead tip with a case reference. An additional implantable loop recorder (ILR) near the LA recorded single lead electrograms. Interrogation of the two devices was performed weekly including spontaneous AF events when available. The Welch's approach to fast Fourier transform (FFT) was used to obtain DFs in a 4-20 Hz band from 5 sec long segments after QRST removal (mean, 4 segments/week per sheep).

Results:

The duration of fast pacing needed to achieve detectable AF was 1-8 weeks. Over the following 12 weeks in AF, DF values in the ILR and RA lead were between 5.7-12.5 and 6-11.5 Hz, respectively. Increase in DF was observed over a 2 week period when the first episode of AF was detected (6.8±0.9 Hz to 10±1.0 Hz, N=3), after which it stabilized. During the 12 weeks of persistent AF, the DF values detected by the ILR were found to be significantly higher than those detected by the RA lead (10.4 vs. 9.3 Hz, respectively. N=5, $P<0.05$). Optical mapping of the hearts after isolation found AF with similar LA to RA difference in DFs. Ex-vivo assessment of LA dimensions and fibrosis confirmed expected dilation and structural remodeling in persistent AF atria.

Conclusions:

We have developed a sheep model of persistent AF with dual-chamber in-vivo electrogram-based monitoring. Detection of the first episode of AF confirms a progressive increase in DF that eventually stabilizes until the end of the 12 week period studied. The different DFs in the two recording leads suggest a stable LA-RA DF difference in this model.

Ronen Jaffe, MD | 10:35-10:50

Strategies for Prevention of Distal Coronary Embolization and Microvascular Obstruction During Coronary Intervention.

Distal coronary embolization (DCE) during percutaneous coronary interventions (PCI) leads to microvascular obstruction (MVO) and myocardial injury and is an independent predictor of adverse outcome. Distal coronary embolization may occur in different clinical settings; in patients undergoing emergency PCI due to acute myocardial infarction (AMI) the embolized material consists mainly of thrombus, while PCI in degenerated bypass grafts (SVG) may lead to embolization of friable plaque. Several device strategies have been developed for prevention of DCE. Aspiration devices remove particulate matter prior to stenting. Distal embolic protection devices (EPD) are deployed prior to stenting, capture particles that are released during stenting and subsequently retrieve them. Randomized trials have studied the efficacy of these strategies in patients undergoing AMI and SVG interventions. In patients undergoing SVG interventions, distal EPD reduced MVO by 67% and adverse events by 42%. However, despite their proven efficacy EPD are used in the US in less than 25% of cases due to device complexity. In patients undergoing emergency AMI interventions, thrombus aspiration decreased MVO by 35% and 1-year mortality by 38%. However, aspiration devices may potentially induce DCE during deployment and do not completely remove thrombus from the culprit vessel. Another approach for DCE prevention consists of proximal EPD whereby the vessel is occluded upstream prior to stenting. Following stenting the static blood column within the vessel which contains the released particles is aspirated prior to renewing antegrade blood flow. Proximal EPD have several potential advantages including protection of side-branches and avoidance of need to cross the unprotected lesion prior to deployment, however a user-friendly intuitive proximal EPD is currently lacking.

Michael Aviram, DSc| 10:50-11:05

HDL– Associated Paraoxonase1 (PON) Inhibits Macrophage Foam Cell Formation and Atherosclerosis Development: beneficial role for Pomegranate (POM) antioxidant.

Paraoxonase 1 (PON1) possesses hydrolyzing activities against atherogenic oxidized lipids, and these activities are related to PON1 histidine (115 &134) diad active site. Macrophage cholesterol accumulation and foam cell formation, the hallmark of early atherogenesis, involves decreased cholesterol efflux. We have shown that HDL – associated PON1 increases HDL binding to macrophages and cholesterol efflux from these cells, via the ABCA1 transporter. In contrast, binding of HDL to the macrophage SR-BI transporter that was also shown to be up regulated by PON1, but PON1 did not affect cholesterol efflux via SR-BI (though it decreased macrophage apoptosis by HDL).

PON1 is inactivated by oxidative stress and upon using potent antioxidants such as the pomegranate polyphenol hydrolysable tannin - punicalagin, in vitro and in vivo, PON1 activity and PON1 - HDL association, significantly increased, resulting in some most beneficial anti atherogenic effects against macrophage foam cell formation and atherosclerosis development. Finally, we analyzed PON1 status in association with protection against atherosclerosis development, also in humans. The intima media thickness (IMT) in patients with proven carotid artery stenosis (CAS) that consumed pomegranate juice (8 ounces a day, for one year), not only did not progressed, but was in fact attenuated by 35%, in parallel with a 90% increase in serum PON1 activity, and in the association of PON1 to HDL . We thus conclude that PON1 is a potent HDL – associated anti – atherosclerotic enzyme due to its ability to breakdown specific oxidized lipids in the atherosclerotic lesion. Up regulation of PON1 by hypo cholesterolemic, anti oxidants, or anti diabetic means, could be the target for atherosclerosis development attenuation.

Ralph Lydic, PhD | 11:05-11:20

Obese rats with features of metabolic syndrome have altered sleep and breathing.

Background: Obese patients with sleep apnea have an increased prevalence of cardiovascular disease (*J Am Coll Cardiol* 57: 1877, 2011). The antecedent causes linking cardiovascular disease, obesity, and sleep are unclear. Sleep fragmentation and deprivation alter hormonal regulation of satiety and can promote obesity (*Chest* 137: 711, 2010). The drive to feed in the absence of caloric need (hedonic feeding), sleep, and breathing all originate in the brain. Yet, the word "brain" is missing from the American Heart Association/American College of Cardiology Foundation list of research priorities (*Circulation* 118: 1080, 2008), and absent in *Lancet's* special issue on obesity (*Lancet* 378:741, 2011). This presentation will highlight a collaborative research program that is addressing this omission by characterizing the neurobiological phenotypes in a rodent model of metabolic syndrome (*Science* 307: 1176, 2005).

Methods and Results: A rotational breeding strategy was started in 1996 to develop lines of rats that differ for intrinsic (untrained) aerobic capacity and retain wide heterogeneity (*Physiol Genomics* 5: 45, 2001). The lean/fit rats weigh 300 to 350 g and the obese/metabolic syndrome rats weigh 500 to 600g. The run-to-exhaustion distance for lean/fit rats is about 2000 m and about 250 m for the obese/metabolic syndrome rats. To date we have demonstrated that the metabolic syndrome rats have disordered sleep, prolonged recovery from peripheral nervous system injury, and altered nociception. Obese patients are at increased risk of respiratory problems when administered sedative/hypnoptic drugs. Ongoing studies are testing the hypothesis that sedative/hypnotic drugs depress breathing and alter acetylcholine release in the brains of metabolic syndrome rats.

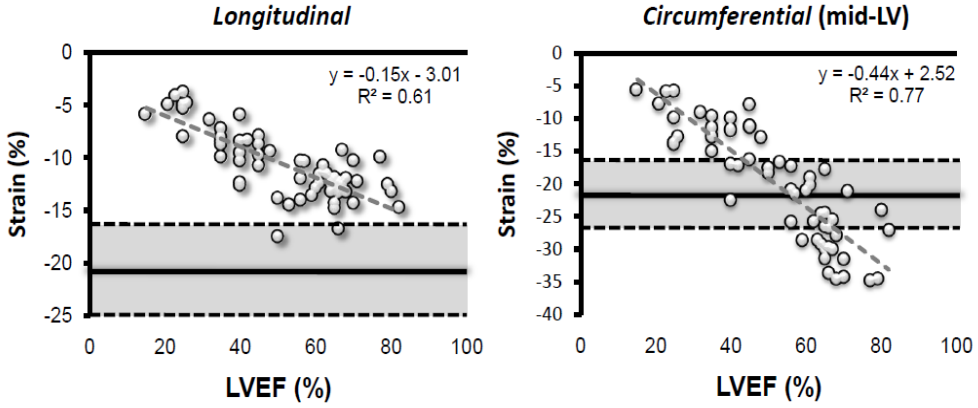
Support: NIH Grants: HL40881 & HL65272; Department of Anesthesia

Yoram Agmon, MD | 11:20-11:35

Novel Insights into Cardiac Function Using Echocardiographic Myocardial Deformation (Strain) Imaging: Differential Multiplane Cardiac Dysfunction

Background: Left ventricular (LV) deformation and rotation can be quantified in multiple planes using echocardiographic two-dimensional strain (2DS) imaging. The objectives of our studies were: 1) to measure LV strain in multiple planes in patients with severe aortic stenosis (AS) before aortic valve replacement (AVR); 2) to determine the changes in LV strain in multiple planes following AVR; 3) to examine the relationship between LV strain and LV ejection fraction (LVEF) in these patients.

Methods and Results: Long-axis strain, short-axis strain and apical rotation were measured by 2DS before and early (7±3 d) after AVR in 45 patients with severe AS and preserved LVEF (≥50%). At baseline, longitudinal strain (LS) was lower and circumferential strain (CS) was higher, compared to controls. These changes partially reversed after AVR. This increase in CS was not evident in 32 patients with LVEF <50% (Figure; normal range in grey). Apical rotation was higher in patients with moderately reduced LVEF (35 %< LVEF<50%), compared to patients with preserved LVEF or severe LV dysfunction (LVEF ≤35%).



Conclusions: Multiplane assessment of LV deformation in patients with AS demonstrates differential long-axis dysfunction. Compensatory mechanisms (increased CS and apical rotation) are gradually lost with reduced LVEF.

References:

1. Carasso S, Agmon Y et al. Differential effects of afterload on left ventricular long- and short-axis function: Insights from a clinical model of patients with aortic valve stenosis undergoing aortic valve replacement. *Am Heart J* 2009;158:540-5.

2. Carasso S, Agmon Y et al. Relation of myocardial mechanics in severe aortic stenosis to left ventricular ejection fraction and response to aortic valve replacement. *Am J Cardiol* 2011; 107:1052-7.

Theodore J. Kolias, MD | 11:35-11:50

Advances in the Echocardiographic Assessment of Cardiac Function.

Strain rate imaging using speckle tracking echocardiography (STE) may provide a more straightforward and accurate assessment of systolic and diastolic function than conventional parameters. Current commercial systems, however, have limitations when measuring strain rate because of low speckle tracking frame rates (typically < 100 frames/sec). We have been working with industry collaborators (Epsilon Imaging Inc.) to develop a prototype radiofrequency (RF)-based STE system that can perform speckle tracking at very high frame rates (> 500 frames/sec), with an effective temporal resolution of 62-67 frames/sec. This prototype uses the raw RF data (including the signal phase information) to optimize tracking.

We used this prototype system to evaluate diastolic function in 36 patients. Global peak longitudinal early diastolic strain rate (dSR) was determined for each patient. Standard echocardiography (performed on the same day using a commercial system) was used to assess for the presence (DD+) or absence (DD-) of diastolic dysfunction. Global dSR was significantly lower in DD+ than in DD- ($1.11 \pm 0.46\ s^{-1}$ vs. $1.64 \pm 0.57\ s^{-1}$; $p = 0.005$). Global dSR < 1.00 had a sensitivity of 65% and a specificity of 88% for prediction of diastolic dysfunction defined by standard criteria (area under the curve = 0.782, $p = 0.005$). We concluded that RF-based STE using the new prototype provides a novel measure of diastolic function, and may potentially allow for better diagnosis of diastolic dysfunction as well as improved assessment of therapeutic interventions for diastolic heart failure.

Finally, with our industry collaborators, we have also been developing new B-mode speckle tracking software that can be applied to any DICOM format 2-D image. This software allows strain rate analysis and comparison of images obtained from different systems, as well as retrospective analysis of previously performed echocardiograms. As such, this new technique has significant clinical and research potential.

Uri Rosenschein, MD | 1:10-1:25

Ultrasound Thrombolysis – Waves, Bubbles & Clots.

We have studied the mechanical effects of high-power low-frequency ultrasound (HPLFU) in the last 20 years. Early work suggested that clots are rapidly liquefied by HPLFU while arterial wall is resistant. Obstacles in acoustic energy delivery were solved and a catheter-based HPLFU delivery system was developed. *In vitro* and *in vivo* studies in thrombus-rich lesions were followed, in the mid 90's, by a feasibility study in anterior STEMI and occluded LAD arteries. The study suggested that ultrasound thrombolysis (UT) is safe and effective during Primary PCI (PPCI). Unfortunately, at the same period GP IIb/IIIa inhibitors and stents were used successfully in PPCI while other thrombectomy systems trials were negative. Hence, a need for UT was not perceived. A European Registry in various thrombus-rich lesions presentations suggested that SVG lesions may be the appropriate target. Thus, a multicenter clinical trial in ACS patients with culprit lesion in SVG was initiated in the US. Final analysis revealed increased incidence of MACE in the UT group.

In parallel we have explored the potential use of external UT. *In vitro,* effective thrombolysis was attained after optimization of acoustic parameters (e.g. focusing, pulsing). During External UT, clots underwent efficient and rapid liquefaction. The lack of guidance system limited the potential for cardiac application.

During the late 2000's more groups have used non-focused external ultrasound and r-TPA for STEMI. *In vivo* studies were very promising. Yet, the need for thrombolytic agents and ~90 min delay of ultrasound application made this approach irrelevant in the era of PPCI.

The use of ultrasound and r-TPA has showed superior reperfusion rates and clinical outcome, compared with r-TPA only, in stroke patients. Yet, even with adjunct ultrasound, reperfusion is obtained in only ~40% of patients after 120 min. Attempts to increased efficacy by higher ultrasound intensity and r-TPA led to increased rate of intracranial bleeding.

We are currently perusing the use of focused HPLFU under imaging guidance without thrombolytic agents for effective and rapid throbolysis in stroke patients.

Conclusion: Effective translational process, convergence with exact sciences and engineering and appropriate medical need should be optimized in the development of medical technology.

Jordan Shavit, MD, PhD | 1:25-1:40

Identifying Modifiers of Thrombosis Using Zebrafish Models.

Pathologic thrombosis is a leading cause of morbidity and mortality in the developed world. Though susceptibility to thrombosis is primarily determined by genetic factors, many of the responsible genes and genetic variants remain unknown. Unidentified modifier genes contribute to the variable disease severity and penetrance observed among patients and families with thrombophilic risk factors. Identification of such modifiers could help identify patients at higher risk for thrombosis and recurrence, and serve as potential targets for therapy. The zebrafish is a powerful genetic model in which the hemostatic system is nearly entirely conserved with mammals at the genomic level. The ability of this model organism to generate thousands of embryos at a relatively low cost and its amenability to chemical mutagenesis make it a powerful system in which to screen for thrombosis modifier genes. Recent efforts by our group to develop zebrafish mutants in key hemostasis components will be reviewed. Efforts to devise sensitized genome-wide suppressor screens based on these models will also be discussed.

Oliver Kripfgans, PhD | 1:40-1:55

Partial Volume Processing in 4D Cardiac Doppler Flow Estimation.

University of Michigan Cardiovascular Center

Purpose

To test the application of partial volume flow correction in the setting of 4D cardiac Doppler assessment.

Material & Methods

A 4D cardiac scanner (Vivid 7, 3V array, GE Healthcare) was utilized to acquire Doppler in an open-chest sheep- model. In vivo pulmonary artery (PA) flow was acquired with ECG or respiratory gating. A flow cuff (MA20 Transonic) was employed for gold standard reference. Time-averaged flow was recorded using 50 non-ECG gated volumes while ventilator was stopped. Time-resolved flow (48 steps in cardiac cycle) was acquired in ECG-gated mode with continuous respiration. Partial volume processing (PVP) involved Doppler power histogram analysis. 100% blood- filled voxels contribute to maximum Doppler power. Partially filled voxels scatter fractionally less relative to fill-fraction. If represented in sufficient numbers, these 100%-blood voxels form a peak in the Doppler-power histogram. Color flow constant-depth plane (C-plane) resolution was 3, 2.25, and 6.25 pixels/cm in lateral, elevational, and axial directions, respectively. Frame rates were up to 10 Hz. Volume flow was computed using Gauss' theorem by C-plane surface integration and described PVP.

Results

Time-resolved PA flow estimation was within 2.3% to the invasive gold standard. Non-PVP processed data yield 50 to 100% higher flow readings. PA waveform indicated delayed time-to-peak compared to aortic waveform.

Conclusion

Similarly to cardiac MRI, PVP is essential in cardiac flow imaging. Doppler power serves as a non-invasive method without the need for contrast injection.

Acknowledgements:

Cardiovascular Center McKay Grant Award, Cardiovascular Center Heart of a Champion Award, NIH-NHLBI R01 HL067921, General Electric Research Gift

Benedict R. Lucchesi, MD, PhD | 1:55-2:10
And Jullia Y. Lee

University of Michigan Cardiovascular Center

Inhibition of the thromboxane A_2 (TxA_2) receptor and thrombin maintains vessel patency after thrombolysis with alfimeprase vs. rt-PA.

Background: Alfimeprase is a direct acting fibrinolytic enzyme and a recombinant variant of fibrolase—a zinc metalloproteinase purified from snake venom. In contrast to clinically available thrombolytic agents, alfimeprase induces rapid thrombolysis and does not promote hemorrhagic complications in patients with peripheral arterial occlusions most likely due to its rapid inactivation by alpha2-macroglobulin. Here, we investigated the therapeutic potential of alfimeprase using a carotid arterial thrombosis animal model.

Methods: In anesthetized beagles, carotid artery thrombosis was induced by electrolytic endothelial injury. After 30 minutes of occlusion, animals were treated with vehicle, S18 (TxA_2 receptor antagonist), and/or hirudin (direct thrombin inhibitor). Thrombolysis was induced by alfimeprase or recombinant tissue plasminogen activator (rt-PA), and vessel patency was monitored for 90 minutes.

Results: The onset to reperfusion was more rapid in animals treated with alfimeprase than rt-PA. All the animals treated with hirudin+S18+alfimeprase maintained vessel patency, and all vehicle-treated animals reoccluded. In the group treated with hirudin+S18+alfimeprase, time to reocclusion and total reflow time after thrombolysis were longer compared to vehicle-treated animals. The quality (i.e. a modified TIMI score) and quantity of blood flow were most improved in animals treated with hirudin+S18+alfimeprase. There were no significant differences in time to reocclusion, total reflow time, and quality and quantity of blood flow between vehicle+rt-PA treated animals and hirudin+S18+rt-PA treated animals.

Conclusions: Inhibition of thrombin and the TxA_2 receptor enhances the thrombolytic activity of alfimeprase, sustaining vessel patency without the induction of a systemic lytic effect.

Yoav Turgeman, MD | 2:10-2:15

CaRdiovascular and Echocardiographic Assessment in hyperteTION during Pregnancy: CREATION –P Study.

Aim: Assessing cardiac structure and function including echocardiographic parameters for predicting the course of pregnancy among hypertensive women

Patients and Methods: We conducted a prospective study of 60 women with chronic hypertension who underwent routine echocardiography during the 2ed or 3rd trimester. Thirteen were treated with labetalol, 16 with methyldopa, and 31 were without treatment. We compared the echocardiographic findings to 31 healthy pregnant women of similar gestational ages. Demographic characteristics and obstetrical history did not differ between the groups. Women were followed up until discharge after delivery. Assuming abnormal echo findings in 50% of the study group and 20% in the controls, power analysis showed that 60 and 30 women were needed in a rate of 2:1, respectively, with alpha=0.05 and power of 80%. The study was approved by the local ethical committee and women signed informed consent before enrollment.

Results: Two dimentional and Doppler echocardiography has revealed in both groups normal size of cardiac chambers, normal systolic left ventricular ejection fraction, no signs of hypertrophy, and normal flows without significant valve regurgitation. Diastolic dysfunction was found in 63% of the study group vs 29% of the controls (P=0.004, OR=4.2, 95% CI 1.7-10.8). Superimposed preeclampsia was diagnosed in 25% of the study group vs 3% of the controls (P=0.009). There were no differences in the rate of diastolic dysfunction and superimposed preeclampsia in the sub-groups of women with chronic hypertension. Thirteen of the 38(34%) patients with chronic hypertension and diastolic dysfunction had superimposed preeclampsia compared with 2/22 (9%) patients without diastolic dysfunction (P=0.03, OR=5.7, 95% CI 1.2-28.2). Other obstetrical parameters did not differ between the groups.

Conclusion: Echocardiography done routinely in pregnancy to women with chronic hypertension revealed a high rate of diastolic dysfunction, which was associated with superimposed preeclampsia.

Jeffrey L. Platt, MD | 2:25-2:40

And Marilia Cascalho

University of Michigan Cardiovascular Center

Impact of cardiac transplantation on the immune system of the young.

Cardiac transplantation can correct the devastating physiology of congenital heart disease and cardiomyopathy in the newborn. However, cardiac transplantation typically includes removal of the thymus and medical therapies that deplete mature T cells and suppress the functions of T cells that remain. Since T cells develop only in the thymus, these manipulations should cause profound contraction of diversity of T cell antigen receptors (TCR) and impose severe immunodeficiency. Consistent with this prediction, we previously reported that those who have undergone cardiac transplantation in infancy frequently exhibit a lack of recent thymic emigrants in their blood and a profound contraction of TCR diversity (from ~10^9 to 10^3). Since host defense theoretically depends on TCR diversity, this contraction should compromise the wellbeing of transplant recipients, perhaps causing dissemination of viral agents, opportunistic infection and graft versus host disease. Contrary to this prediction and to the widely accepted concept, however, we find that recipients of heart transplants in infancy are generally well, exhibiting none of the opportunistic and disseminated infections observed in those observed with repertoire contraction caused by inherited immunodeficiencies. Recipients do exhibit persistent replication of gamma herpes viruses but these defects are not associated with clinical disease. The unexpected wellbeing of cardiac transplant recipients might be explained if residual TCR can exert plasticity of recognition. Consistent with this concept we found that a murine TCR manifestly tolerant to self-MHC (H-2d) could, when expressed by a mouse of a foreign MHC (H-2b), reject vigorously organs bearing the original self-MHC (H-2d). Thus, heart transplantation in infancy may reveal heretofore-unrecognized capacity of T cells to recognize new antigens, including self-antigens, and mount protective or pathogenic immune responses. For want of better term we refer to this capacity as “post-graduate education.”

David Bach, MD | 3:00-3:15

Un-operated Patients with Severe AS or MR: Barriers to Appropriate Management.

Background: Severe symptomatic valve diseases are known to have poor outcomes without intervention. This study tested whether patients with severe aortic stenosis (AS) or severe mitral regurgitation (MR) undergo appropriate referral for surgical intervention, and investigated barriers to intervention.

Methods: Patients with severe AS (mean gradient > 40 mm Hg or effective orifice area < 1.0 cm^2) on echocardiography performed during 2005 at the University of Michigan were retrospectively identified. Medical records were reviewed for comorbid conditions, symptoms referable to AS, and referral for surgery or rationale not to refer. A collaborative effort acquired similar data for patients at neighboring major cardiovascular programs in Washtenaw County. A related study evaluated patients at the University of Michigan with echocardiography/Doppler evidence of severe MR.

Results: Of 368 patients with severe AS at three medical centers, 188 (49%) underwent surgery and 191 (51%) did not. Of 191 un-operated patients, 65 (33%) were asymptomatic and 126 (66%) had symptoms referable to severe AS. The dominant reasons for lack of referral of symptomatic patients were excessive operative risk (48%), patient refusal (19%), and symptoms felt not due to AS (19%). However, the calculated median operative mortality risk (STS) for symptomatic un-operated patients was 3.8% (IQR 2.1 to 7.3%), and 70 (56%) of 126 patients had a calculated operative risk ≤ 5%. Additional investigation at 10 medical centers across the US revealed that predictors of failure to refer for surgical evaluation included older age, lower mean gradient, and symptoms *other than* chest pain.

Investigation of un-operated patients with severe MR revealed a high prevalence of ACC/AHA class I or class IIa indications for intervention.

Conclusion: Many patients with severe symptomatic heart valve disease do not undergo evaluation for intervention. Reasons are complex, including probable subjective over-estimation of operative risks, under-estimation of benefits of intervention in the elderly, and provider bias regarding symptoms and objective data.

Avraham Shotan, MD | 3:15-3:30

Acute Coronary Syndrome in Israel: Data from ACSIS Registry.

In 1990 We started a bimonthly, biannually registry of acute myocardial infaction patients hospitalized in all public cardiology departments. In the 90's we called it The Israeli Thrombolytic Survey. The first decade repeated survey result in an improved therapeutic approach accompanied by a significant reduction in morbidity and mortality. In 2000 we included all acute coronary syndrome patients and named the survey ACSIS. We present the data of 2000-2010 ACSIS surveys of ST elevation MI (STEMI).

	2000	2002	2004	2006	2008	2010
ACS all	1,794	2,048	2,094	2,075	1,763	1,781
STEMI* (%)	708 (71)	649 (54)	675 (51)	699 (45)	589 (47)	688 (50)
Non-STEMI* (%)	296 (29)	552 (46)	658 (49)	739 (55)	665 (53)	686 (50)
STEMI						
Age* (yrs)	63±13	63±13	62±13	63±13	63±13	63±13
Male* (%)	76	78	76	79	81	79
Hypertension* (%)	42	43	48	49	50	56
Current Smokers* (%)	42	40	42	48	48	47
Killip class ≥II* (%)	18	19	19	18	12	12
Thrombolysis* (%)	81	56	32	23	10	3
Primary PCI* (%)	19	44	68	77	90	97
Aspirin, BB, ACE-I/ARB, statin, clopidogrel (4 of 5)* (%)	20	54	78	87	88	92
Length of stay* (days)	7	6	5	5	5	4
Mortality: 7-day* (%)	7.2	4.9	4.3	4.2	3.9	2.7
Mortality: 30-day* (%)	11.1	6.8	6.7	5.8	5.4	4.9
Mortality: 1-year* (%)	15.7	10.7	10.4	10.2	8.1	

*p statistical significant

Conclusion: During 2000-2010 There is a dramatic improvement in the therapeutic approach (primary PCI and evidence bence medications, resulting in a shorter hospitalization, less complication and a significant reduction in mortality.

Maureen Sartor, PhD | 3:30-3:45

Bioinformatics Tool Development for High-throughput Cardiovascular Disease Research.

In the past several years, disease research, including cardiovascular disease research, has greatly benefitted from the revolution in technologies available for high-throughput genomic and epigenomic studies. Such studies now enable researchers to assess genome-wide differential gene expression, SNPs and copy number variations, transcription factor binding profiles, histone modifications, and DNA methylation. Given the deluge of data coming from these experiments, high quality bioinformatics tools are required to maximize knowledge extraction. Although microarrays have been available for gene expression and SNP identification for many years now, we are still working to develop the resources needed to interpret the results of such studies at a systems biology level. Several tools available for cancer research are lacking for cardiovascular research. At an even more premature stage are the tools necessary for deep integration of these high-throughput data types. Researchers are realizing the important role epigenetic mechanisms play in the cardiovascular system, both in response to environmental exposures such as dioxin, as well as to endogenous forces such as circulation and hypoxia. I will discuss some of the bioinformatics tools available and being developed for high-throughput studies, using examples from cardiovascular disease research to highlight their strengths and weaknesses.

John G. Younger, MD | 3:45-4:00

The Fluid Dynamics of Bloodstream Infections.

University of Michigan Cardiovascular Center

In addition to its usual roles in oxygen and nutrient transport, the cardiovascular system occasionally finds itself host to unwanted guests in the form of bacterial pathogens. Blood stream infections are remarkably common (1 in 100 people per year will be diagnosed with bacteremia) and the consequences of bacterial penetration into the cardiovascular system may vary from transient inconvenience to mortal threat. A closely related phenomenon – the infection of intravascular devices – has become a major challenge for both inpatient and outpatient care. Bacteremia is typically considered an immunological event, and considerable understanding exists about the innate and acquired, humoral and cellular responses to blood contact with pathogenic bacteria. Our laboratory however is interested in an invading organism's physical experience in this flowing system, believing that the billions of years of evolution in open bodies of water to which bacteria have been subjected have resulted in responses that likely determine bacterial behavior in the bloodstream. In this discussion I will present a summary of recent results examining important bacterial behaviors (e.g., spontaneous development of multicellular communities, expression of antibiotic resistance) that arise as a function of carefully controlled fluid dynamic exposure and that may have important bearing on our understanding and treatment of life threatening infections of the blood and devices within the bloodstream.

David Ginsburg, MD | 4:00-4:15

Hemostasis in Host Defense from Microbial.

Hemostasis is a critical component of the host response to microbial pathogens and may be an important evolutionary selective pressure underlying the wide variation in plasma level for many blood coagulation factors. Work from our lab characterizing the interaction of the microbial plasminogen activator, streptokinase, with host plasminogen will be reviewed, including recent efforts to modulate this pathway as a novel approach to the therapy of Group A streptococcal infection.

University of Michigan Cardiovascular Center

University of Michigan, Cardiovascular Center
1500 East Medical Center Drive, Ann Arbor, MI 48109

NAME AND TITLE	EMAIL/PHONE
David Bach, MD Park W. Willis III Collegiate Professor of Cardiovascular Medicine and Professor of Internal Medicine	dbach@umich.edu 734-615-4907
Omer Berenfeld, PhD Associate Professor of Internal Medicine, Associate Professor of Biomedical Engineering, Internal Medicine-Cardiovascular Medicine	oberen@umich.edu 734-998-7560
David Ginsburg, MD James V Neel Distinguished University Professor of Internal Medicine & Human Genetics, Warner-Lambert/Parke-Davis Professor of Medicine, Professor of Internal Medicine, Professor of Human Genetics, Professor of Pediatrics & Communicable Diseases, Medical School and Research Professor, Life Sciences Institute	ginsburg@umich.edu 734-647-4808
Jérôme Kalifa, MD, PhD Assistant Professor of Internal Medicine	kalifaj@umich.edu 734-998-7559
Theodore Kolias, MD Associate Professor of Internal Medicine	tkolias@umich.edu 734-615-4907
Oliver Kripfgans, PhD Research Assistant Professor, Radiology, Medical School	greentom@umich.edu 734-647-0852
Ralph Lydic, PhD Bert N Ladu Professor of Anesthesiology Research, Professor of Molecular and Integrative Physiology	rlydic@umich.edu 734-647-7831
Benedict Lucchesi, MD, PhD Professor of Pharmacology	benluc@umich.edu 734-764-9116
Hakan Oral, MD Frederick G L Huetwell Research Professor of Cardiovascular Medicine, Professor of Internal Medicine	oralh@umich.edu 734-615-7271
David Pinsky, MD J Griswold Ruth and Margery Hopkins Ruth Professor of Internal Medicine & Professor of Molecular and Integrative Physiology	dpinsky@umich.edu 734-936-3500
Jeffrey Platt, MD Professor of Surgery and Professor of Microbiology and Immunology	plattjl@umich.edu 734-615-6819
Maureen Sartor, PhD Research Assistant Professor, Center for Computational Medicine and Bioinformatics Research Assistant Professor, Biostatistics	sartorma@umich.edu 734-763-8013
Jordan Shavit, MD, PhD Assistant Professor of Pediatrics and Communicable Diseases	jshavit@umich.edu 734-647-4365
John Younger, MD Associate Professor of Emergency Medicine, Medical School	jyounger@umich.edu 734-647-7564

Technion-Israel Institute of Technology
The Ruth and Bruce Rappaport Faculty of Medicine
1 Efron Street, Bat-Galim, P.O. Box 9649 Haifa 31096 Israel

NAME AND TITLE	EMAIL
Yoram Agmon, MD Senior Lecturer, Ruth & Bruce Rappaport Faculty of Medicine Director, Non-Invasive Cardiology Unit, Rambam Health Care Campus	agmon@rambam.health.gov.il
Ami Aronheim, PhD Associate Professor , Department of Molecular Genetics The B. Rappaport Faculty of Medicine Technion	aronheim@techunix.technion.ac.il
Michael Aviram, DSc Professor of Biochemistry Head, Lipid Research Laboratory, Bernice R. and Joseph Tanenbaum Chair in Preventive Medicine, Senior Vice Dean, Director, The Clinical Research Institute at Rambam	aviram@tx.technion.ac.il
Ofer Binah, PhD Professor of Physiology, Department of Physiology The Sohnis Family Stem Cell Center	binah@tx.technion.ac.il
Ronen Jaffe, MD Senior Lecturer, Interventional Cardiologist, Carmel Medical Center, Ruth & Bruce Rappaport Faculty of Medicine	jaffe@clalit.org.il
Marcelle Machluf, PhD Associate Professor The Laboratory of Mammalian Cell Technology The Faculty of Biotechnology and Food Engineering	machlufm@tx.technion.ac.il
Uri Rosenschein, MD Head, Department of Cardiology Bnai Zion Hospital, Haifa	uri.rosenschein@b-zion.org.il
Eliezer Shalev, MD Dean Ruth & Bruce Rappaport Faculty of Medicine	shaleve@tx.technion.ac.il
Avraham Shotan, MD Head, Department of Cardiology Hillel Yafe Hospital, Hadera	shotana@yahoo.com
Yoav Turgeman, MD Head, Department of Cardiology, Haemek Hospital, Afula and Ruth & Bruce Rappaport Faculty of Medicine	yoav_t@clalit.org.il