New Approaches to Evaluating Maternal Cardiovascular Health in Animal Models

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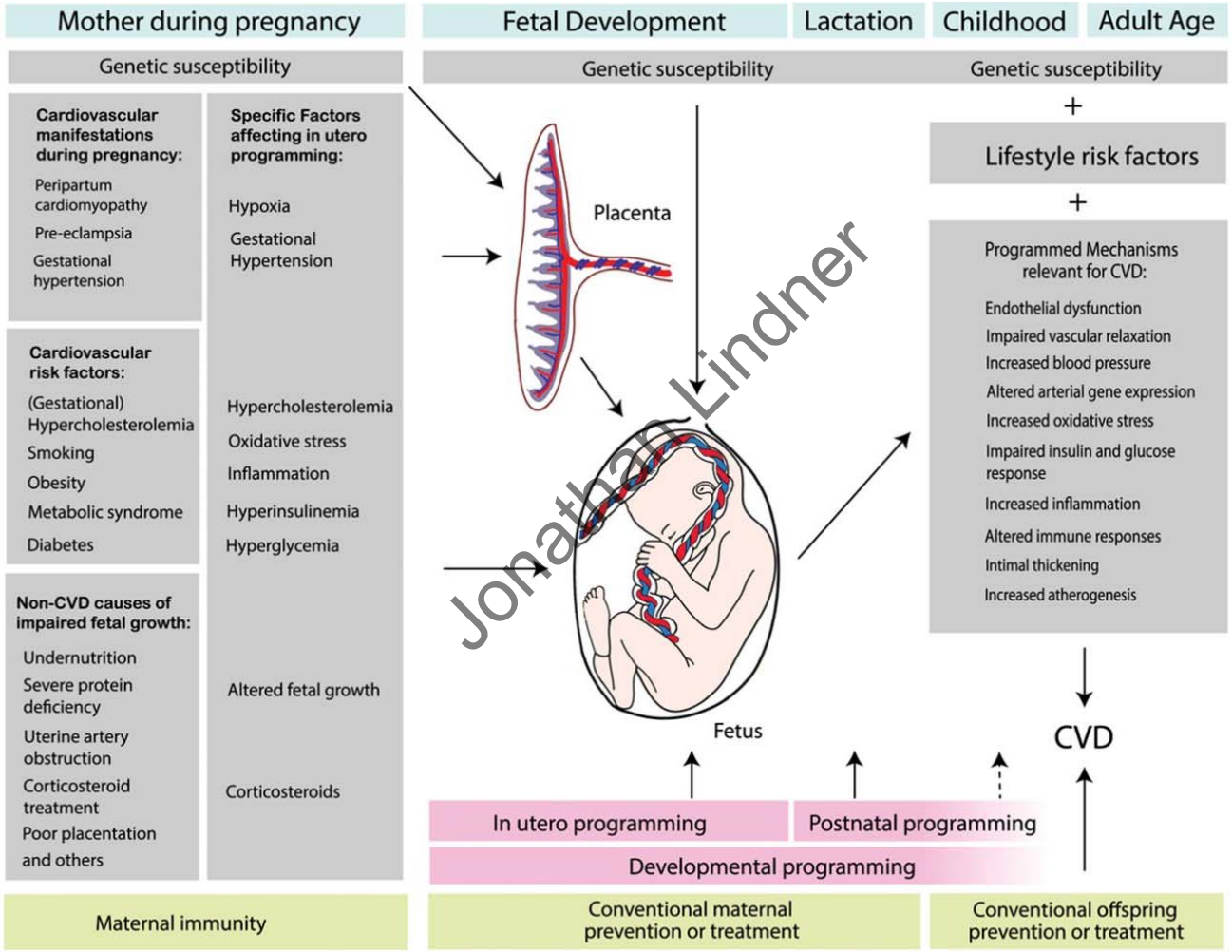
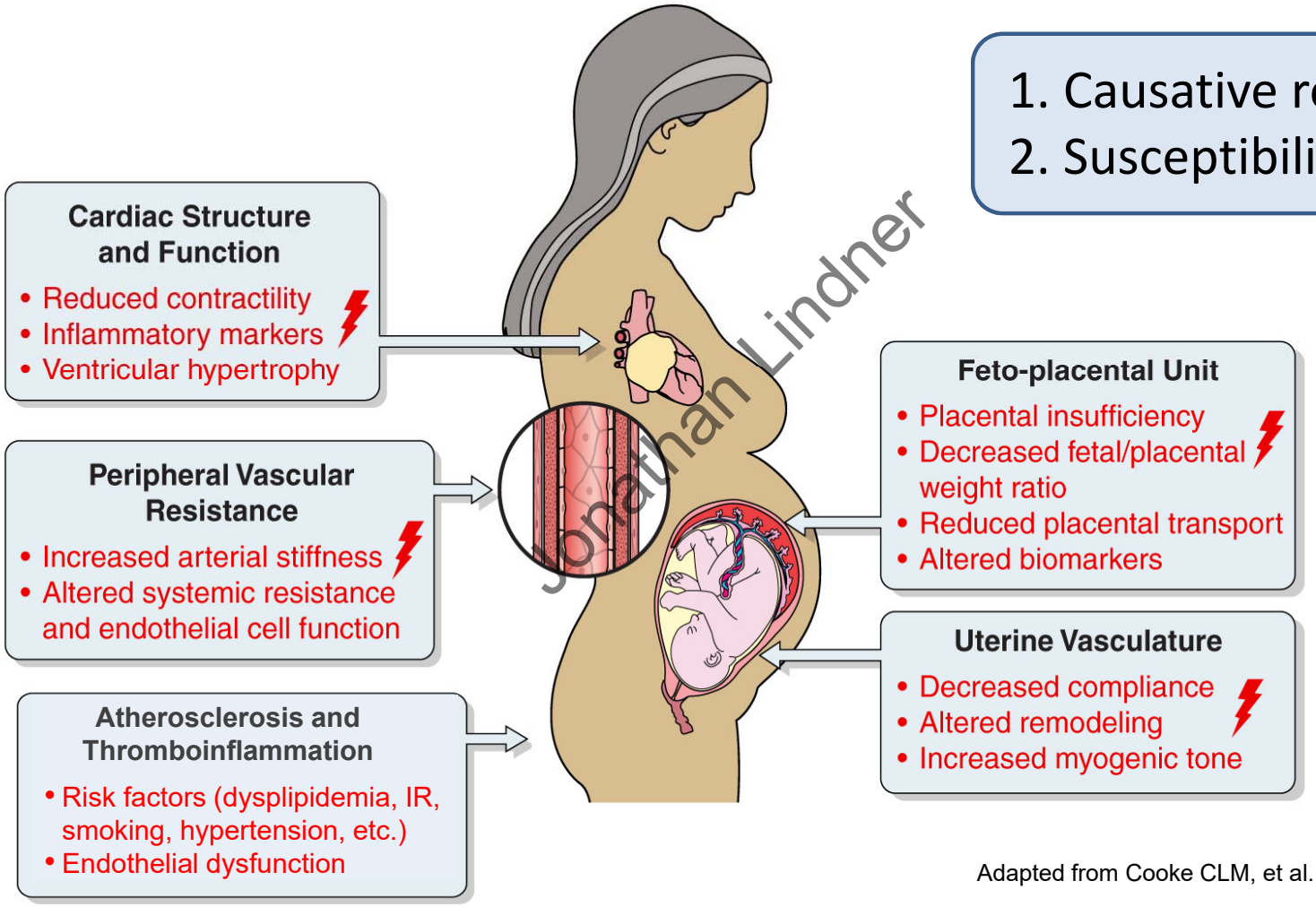
NASA: 18-18HCFBP_1_009
Industry: Lantheus Medical Imaging, Philips

DOHAD With a Focus on the CV System



Palinski W. Circulation. 2014;129,2066

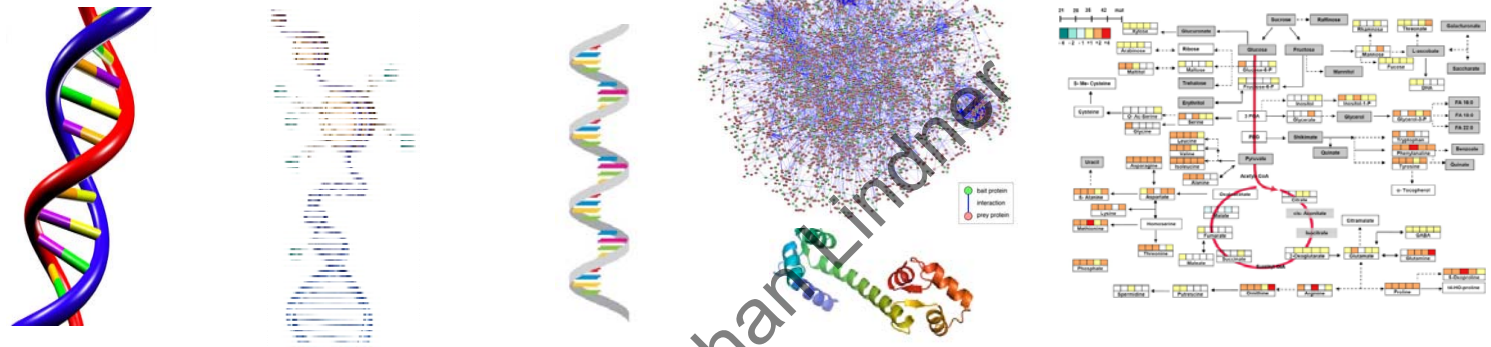
Maternal CV Health and Programming

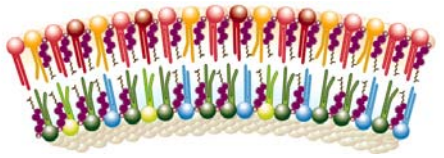


1. Causative relation
2. Susceptibility marker

Adapted from Cooke CLM, et al., Am J Physiol 2019;317:H387

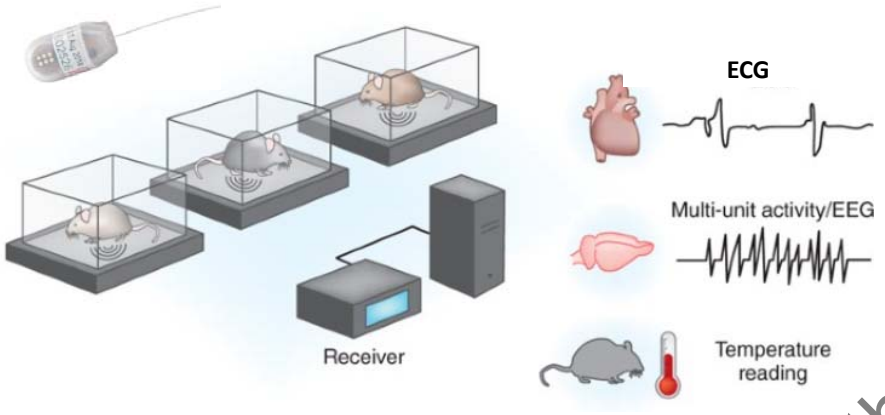
Non-invasive Evaluation of CV System



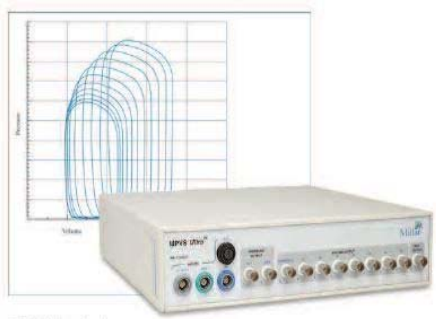


Preclinical Evaluation of CV System: Mice to Monkeys

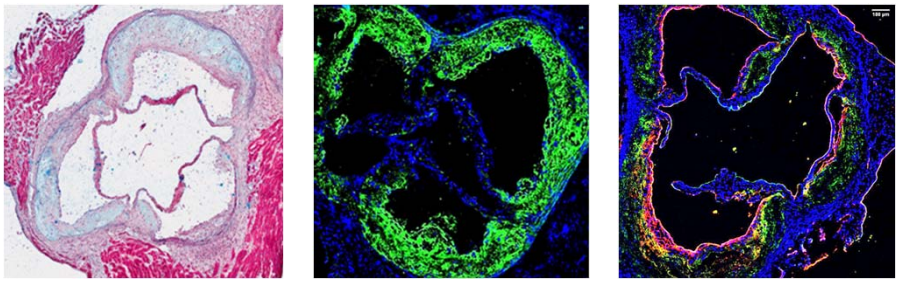
Telemetry



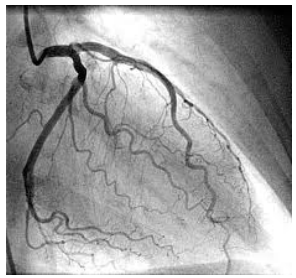
Blood Pressure/PVL



Histology/Ex Vivo



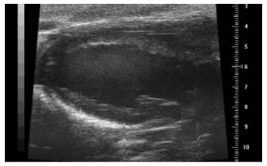
Non-invasive Imaging

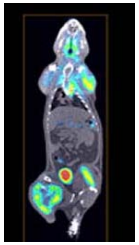


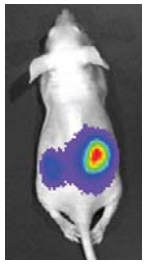
Animal Experimental Imaging Facilities and Cores

Small Animal Research Imaging Core

High Frequency US | **μPET/SPECT/CT** | **Biophotonics**



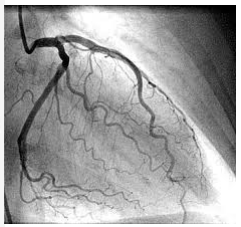
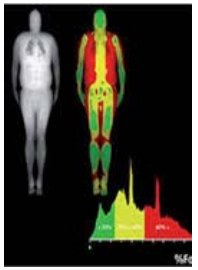





ONPRC Non-human Primate Imaging Centers

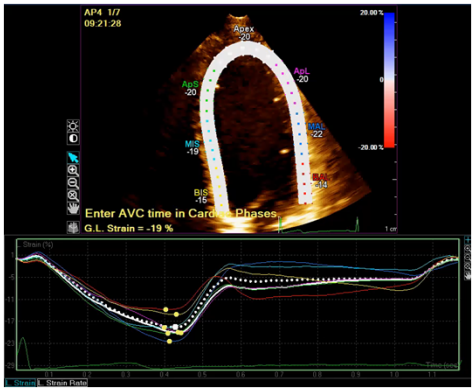
Ultrasound (5) | **PET/CT + SPECT/CT** | **MRI** | **Biplane Angio** | **DEXA**

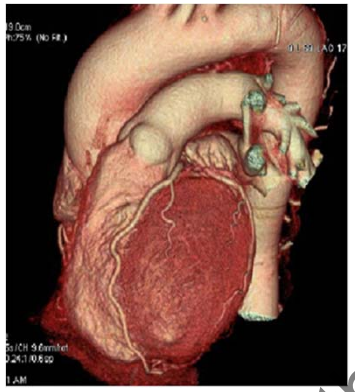


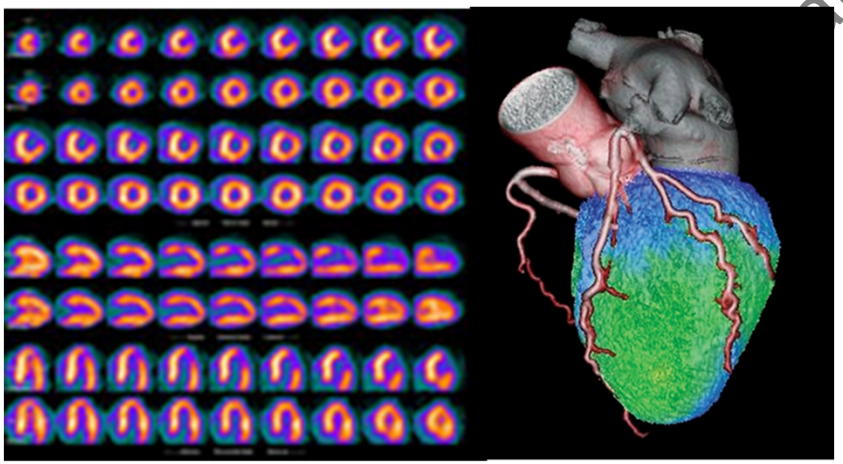




Non-invasive Evaluation of CV System

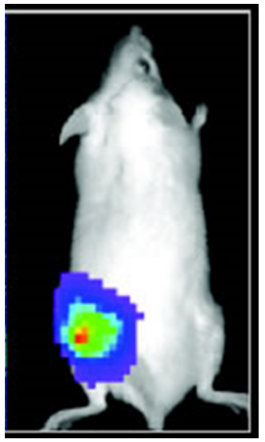
Anatomy & Physiology

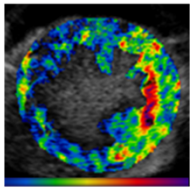


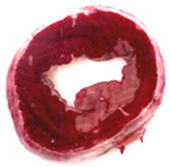


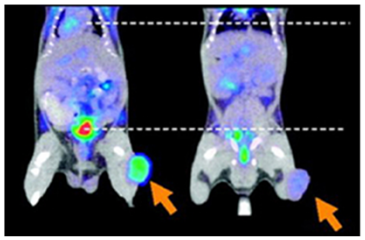


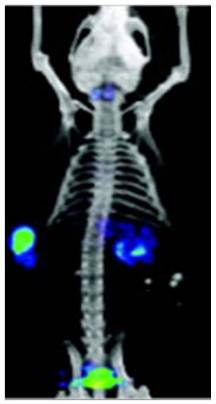
Cell and Molecular Response

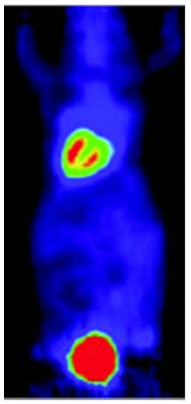












Higher Order Thinking

LV Status

LV Dimensions
LVEF

↓

Stroke volume
Systolic strain
Strain rate
Myocardial work
End-systolic elastance
E/e'
LV mass index

Vascular Status

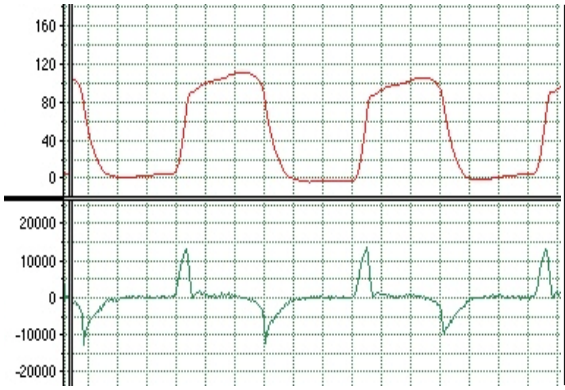
Blood Pressure
Plaque/CIMT Dimensions

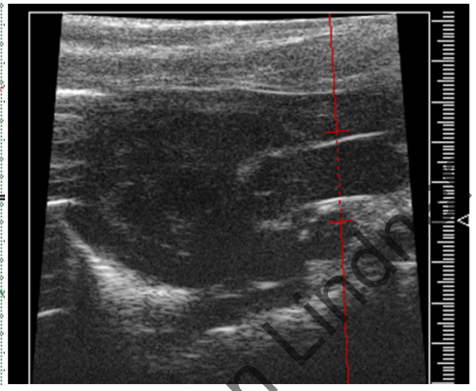
↓

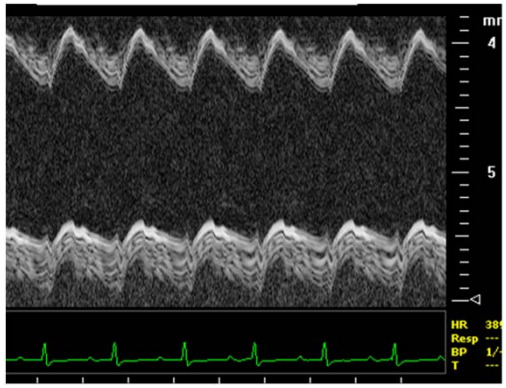
Arterial elastance
Pulse wave velocity
Elastic modulus
Langrangian strain

Ultrasound Measurements of Maternal Vascular Health

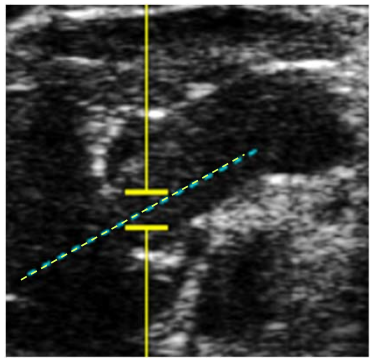
Elastic (Young's) Modulus

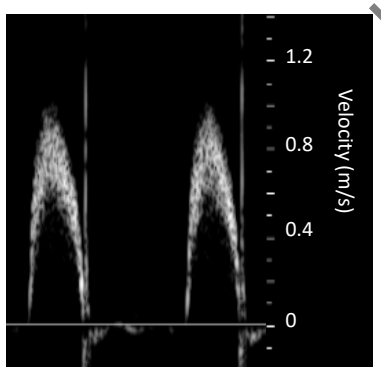


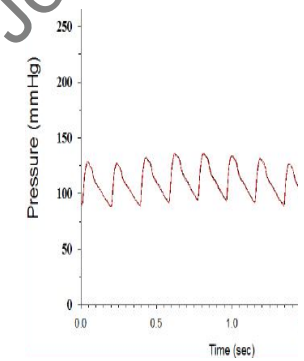




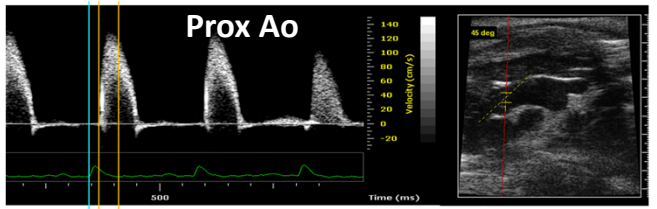
Arterial Elastance

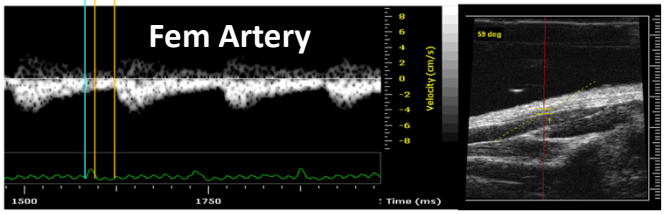




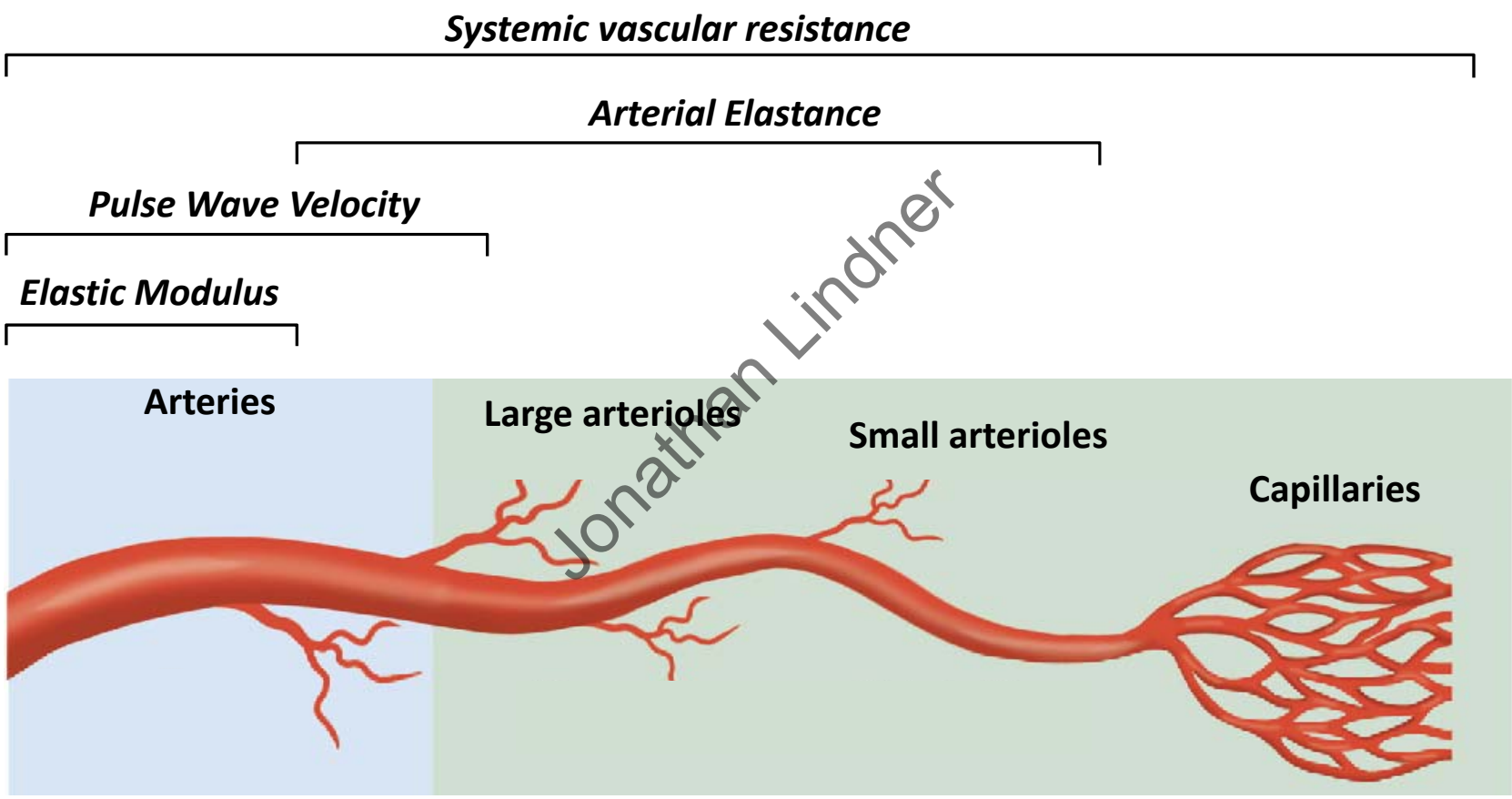


Pulse Wave Velocity

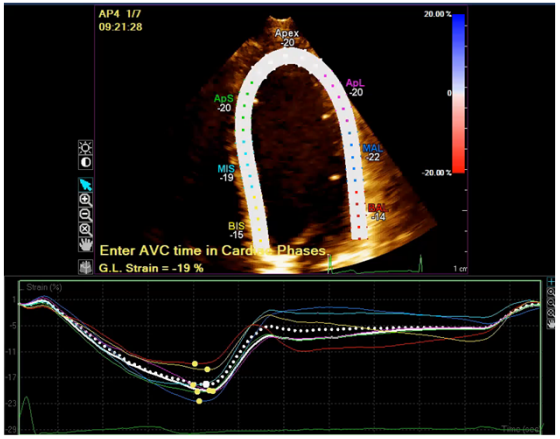




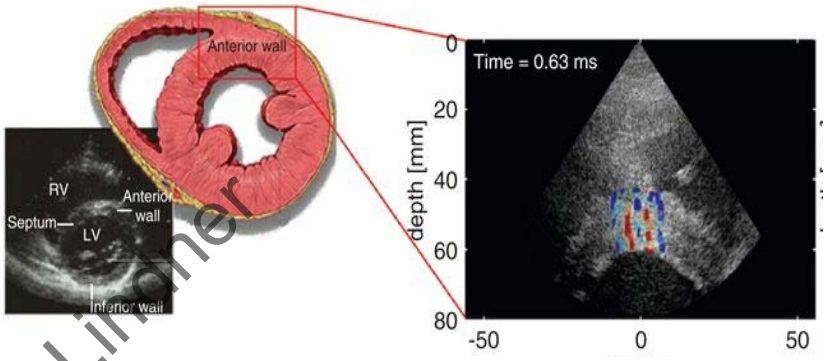
Vascular Status



Advanced Imaging of the Ventricle

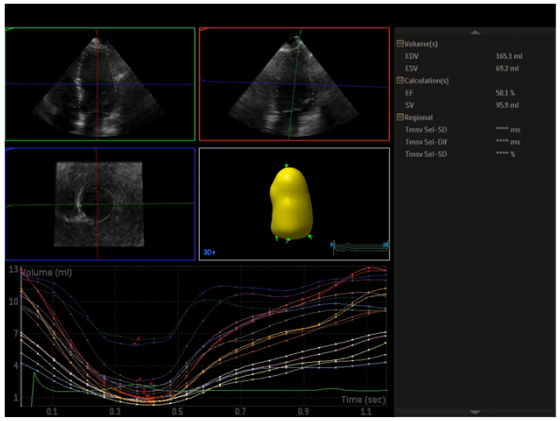


STE Strain Imaging (GLS)

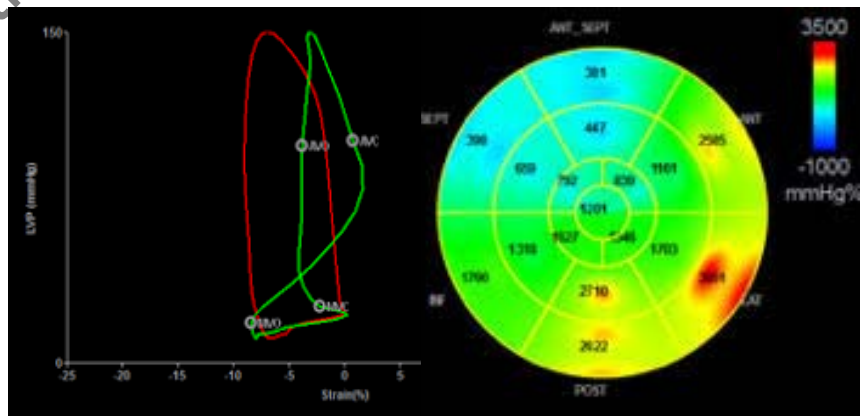


Shear-wave Elastography

Villamain O et al. JACC CVI 2019;12:1146

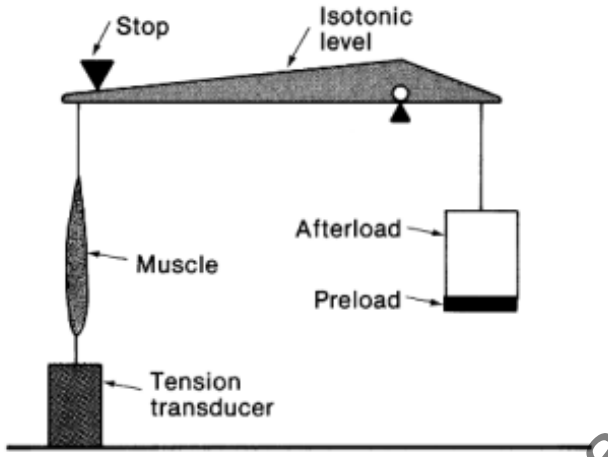


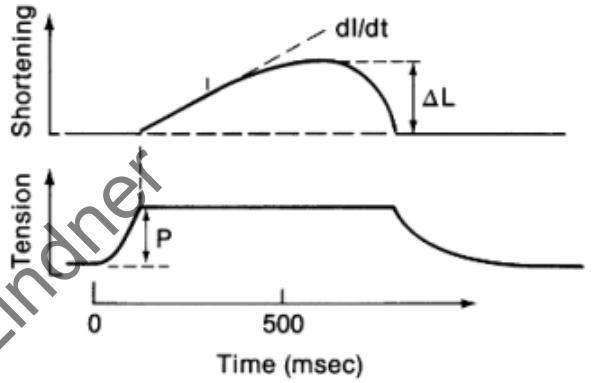
Real-time 3D Volumetric Imaging



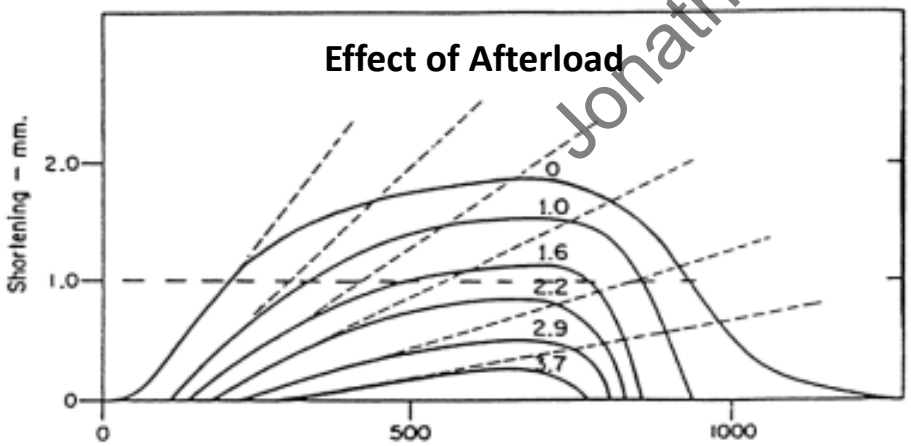
Myocardial Work Index

Afterload and Force-velocity Relations

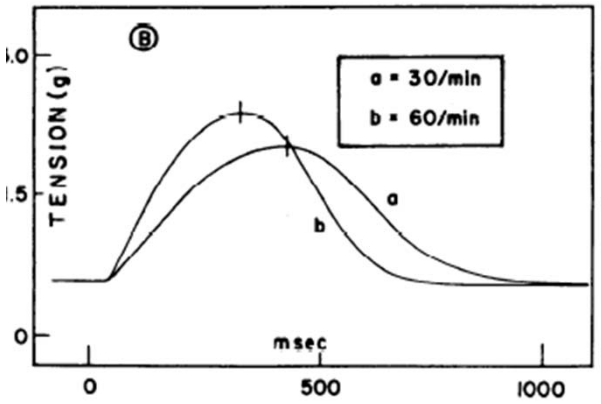




Effect of Afterload



Effect of Beat Frequency

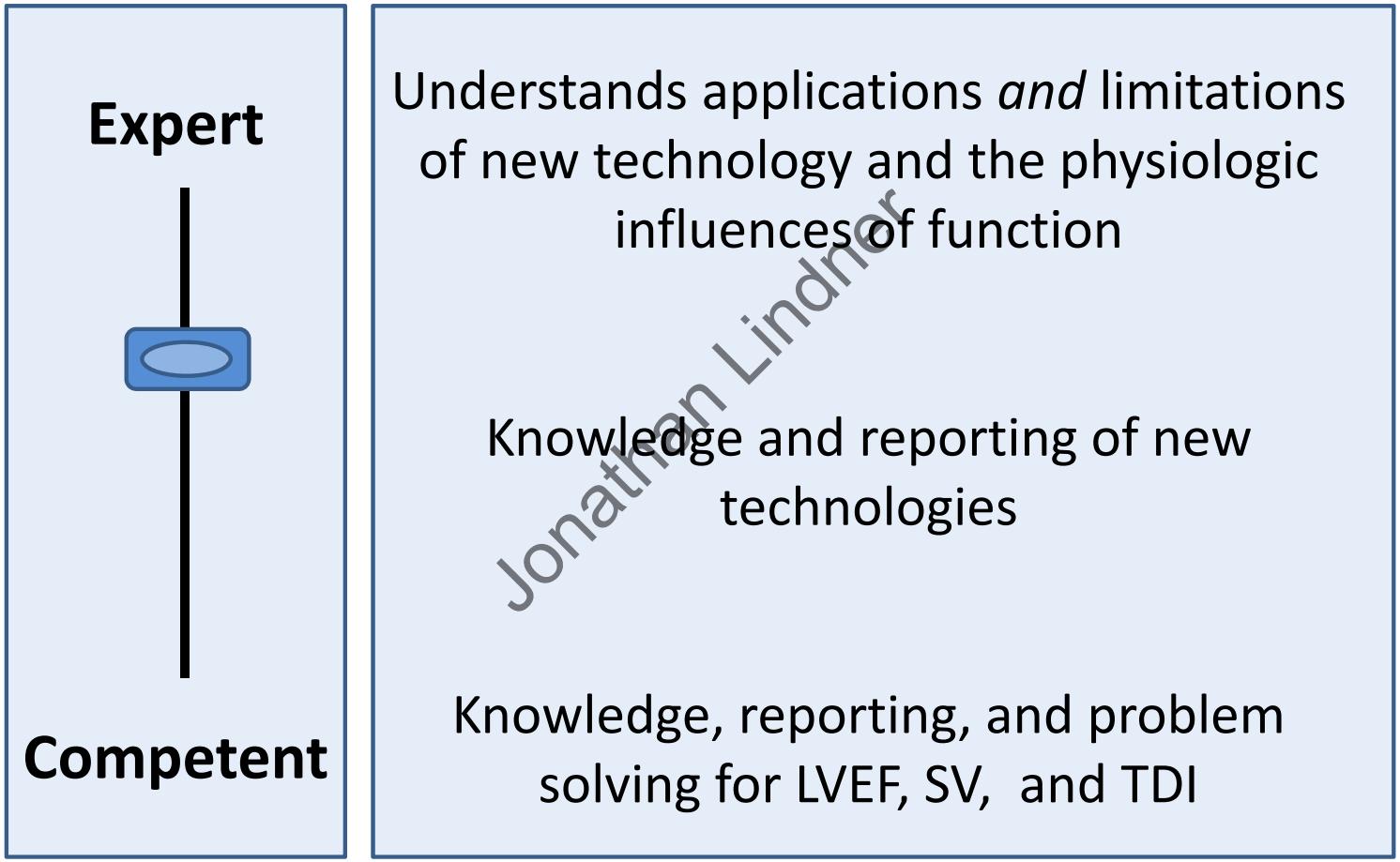


Sonnenblick EH, et al. Am J Physiol 1962;205:931
Sonnenblick EH, et al. Circ Res 1966;19:980

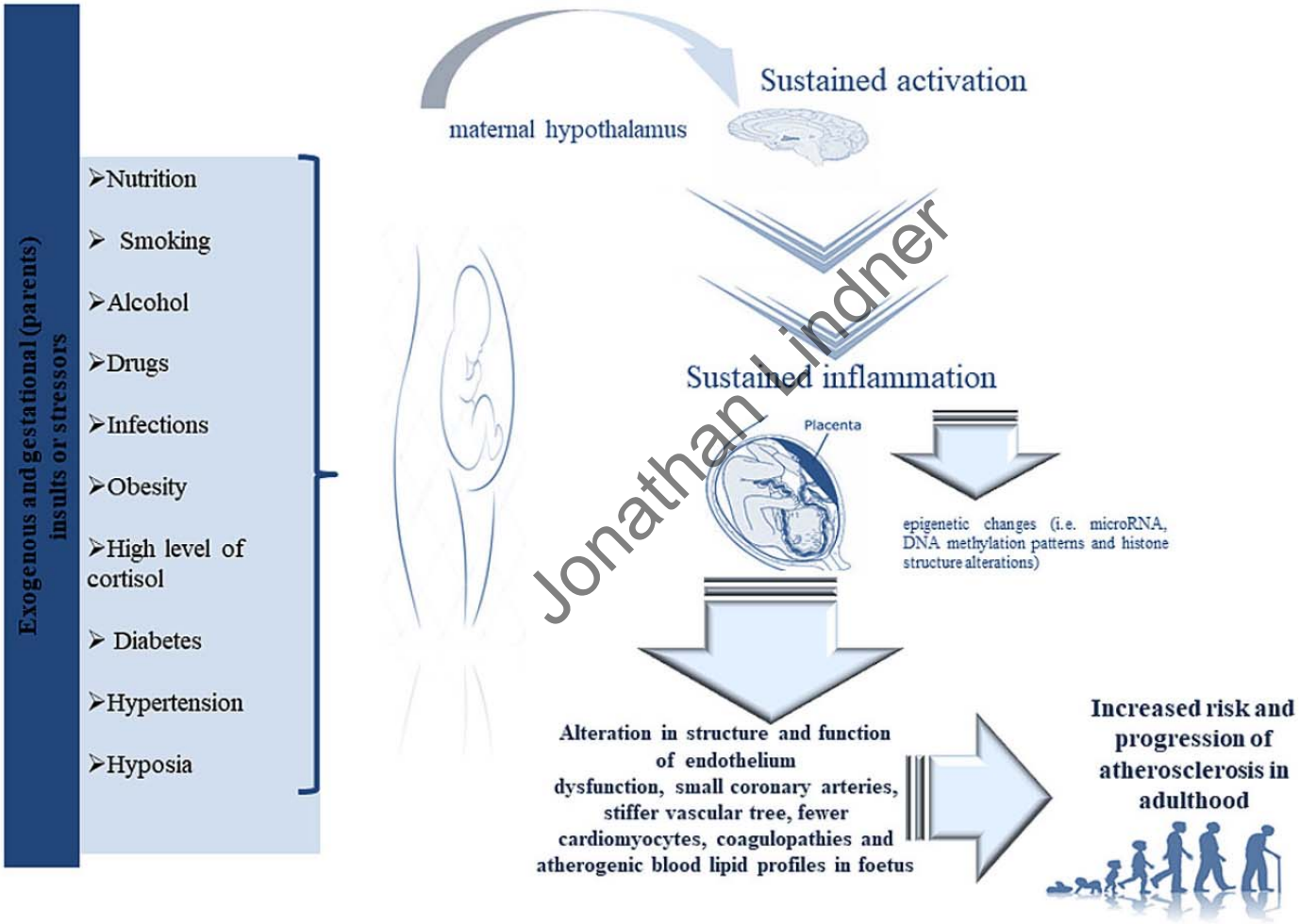
Matching Measurement to Pathway of Interest

Pathophysiology	Best Metric(s)
Decreased LV function	Systolic strain (normalized to load), End-systolic elastance, cardiac output, myocardial work
Hypertrophy	LV mass index, LV mass normalized to afterload, WT/D ratio
Abnormal relaxation or compliance	Transmitral Doppler, E', peak negative strain rate, LV diastolic compliance
Abnormal matrix regulation	Abnormal compliance (above), T1/T2 mapping, Gd kinetics
Abnormal perfusion	Microvascular blood flow normalized to work, microvascular blood volume, BOLD imaging
Abnormal metabolism	PET metabolic imaging, MR spectroscopy

Expert Assessment of LV and RV Systolic Function



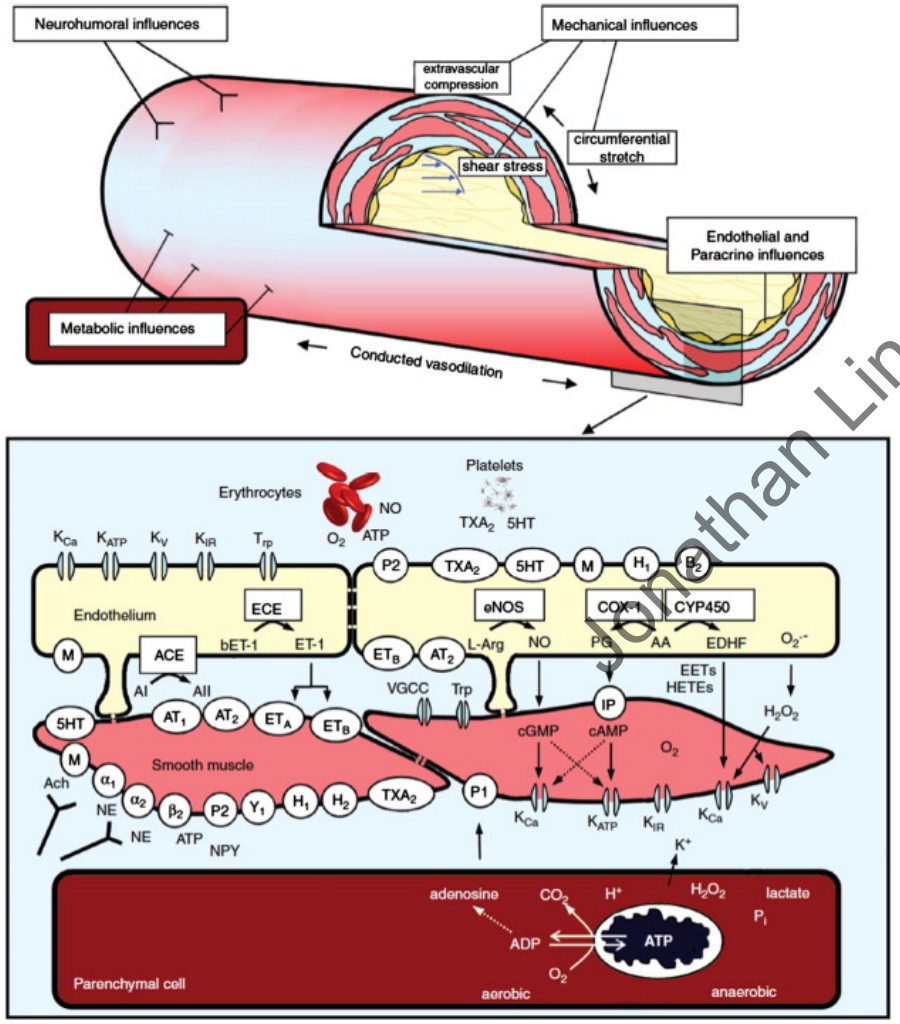
Programmed Origins of Atherosclerosis and Vascular Disorders



Balistreri CR, Cardiovasc Med 2020;23:02113

Regulation of Microvascular Tone

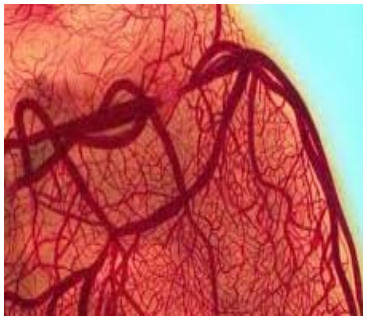
Laughlin MH, et al., Compr Physiol, 2012;2:321



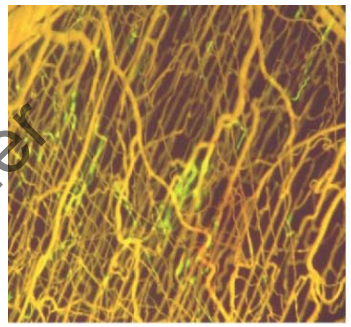
Vasodilation	Vasoconstriction
Nitric Oxide (NO)	Endothelin
Adenosine	Angiotensin II
EETs/HETEs	Thromboxane
H_2O_2	Epi/Norepi
ATP	Dopamine
Prostacyclin	ATP
Bradykinin	Vasopressin
K+	Muscarinic agonists
Histamine	ADMA
VIP	
Anandamide	
Insulin, C-peptide	

Global Assessments of Microvascular Status

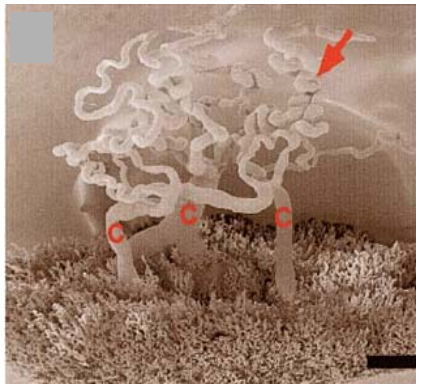
Coronary microcirculation at rest and during stress



Metabolic control of skeletal muscle microcirculation

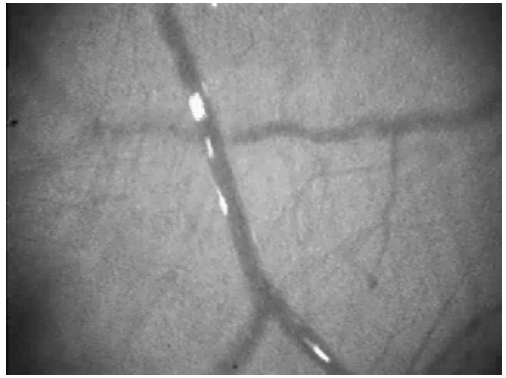


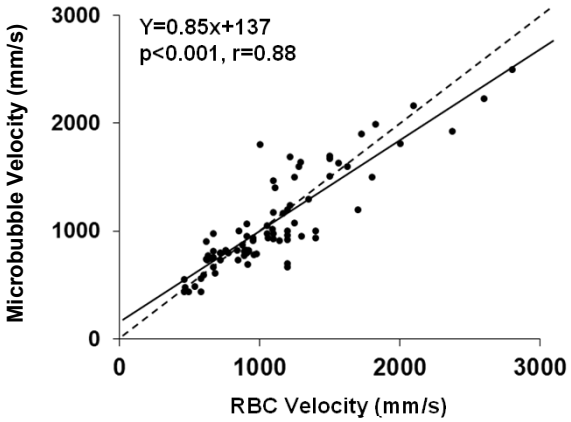
Maternal placental vascular sufficiency



CEU Perfusion Imaging

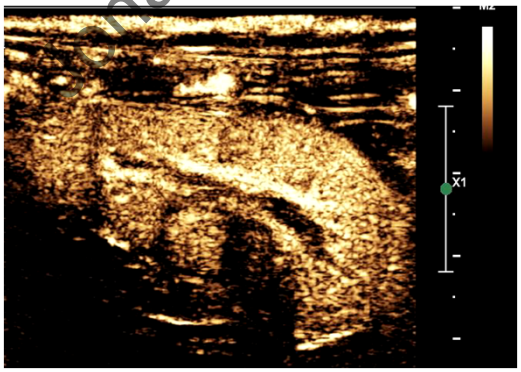
Intravital Microscopy



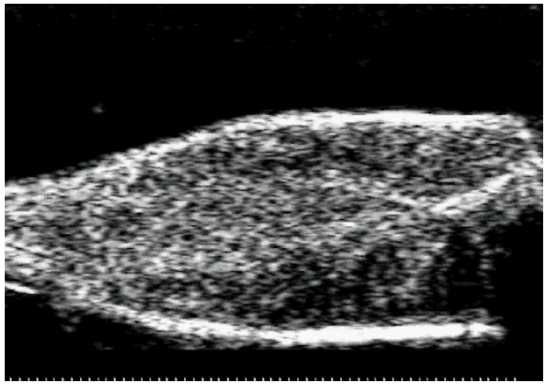


Myocardial Perfusion

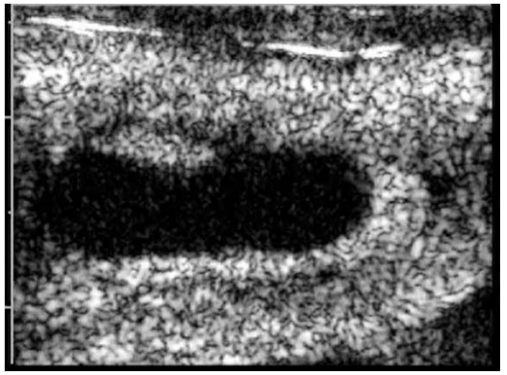
Renal Perfusion



Skel Muscle Perfusion

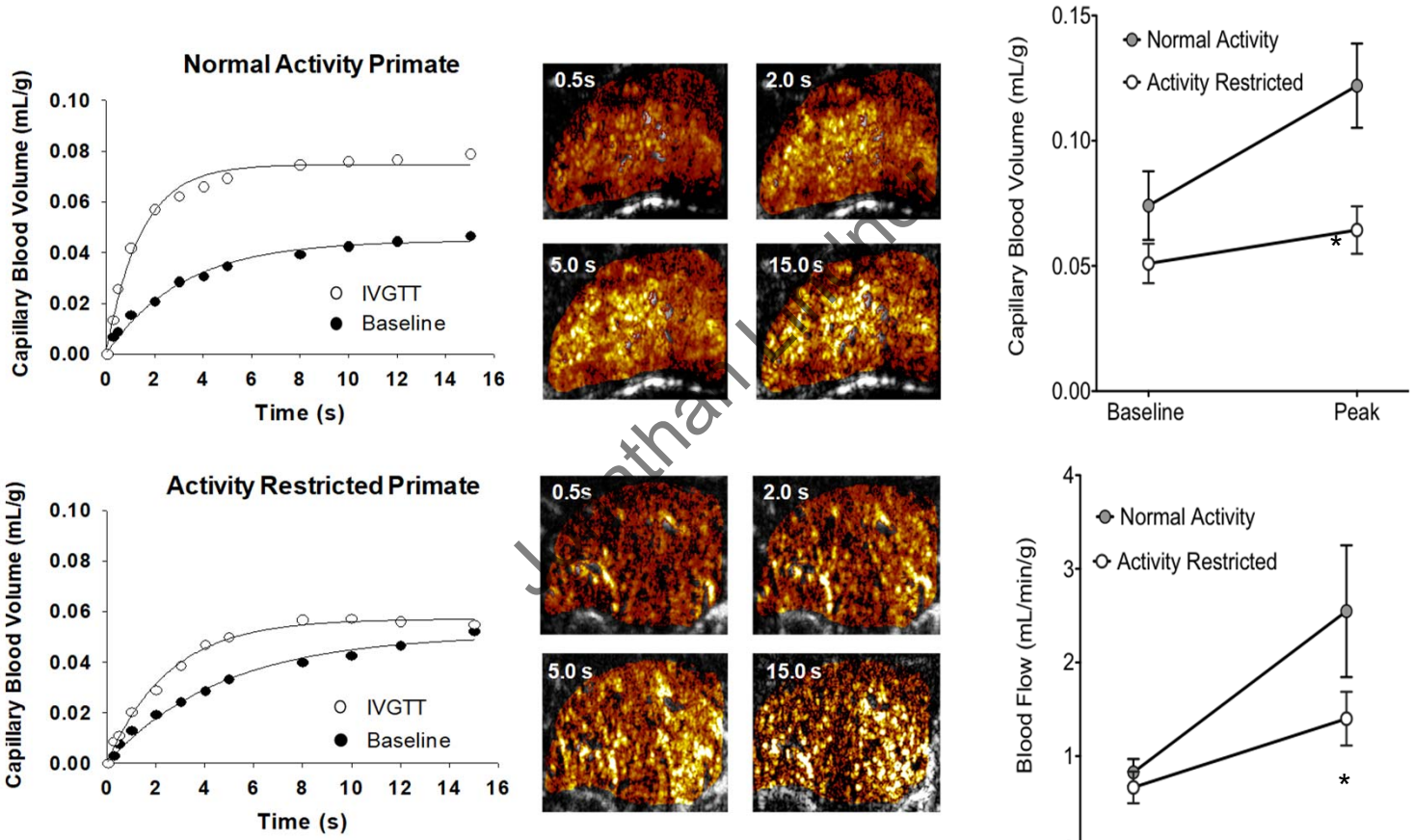


Placental Perfusion



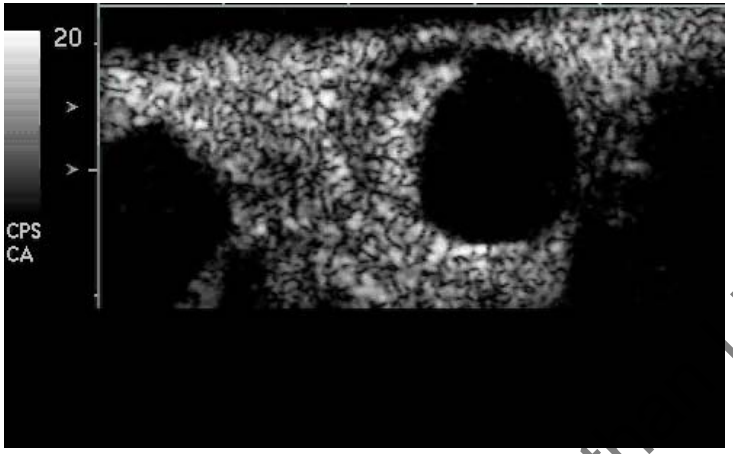
Lindner JR, et al., J Am Soc Echocardiogr 2002;15:396

Assessment of Metabolic Control of the Microcirculation

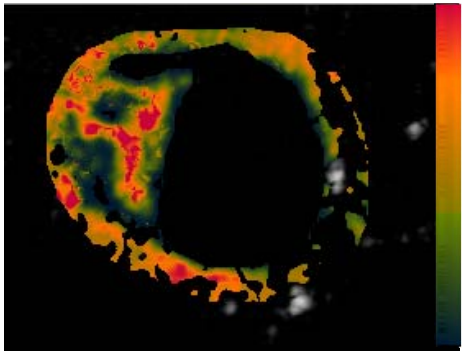


Chadderdon SM, et al., *Am J Pysiol* 2012;303:E607

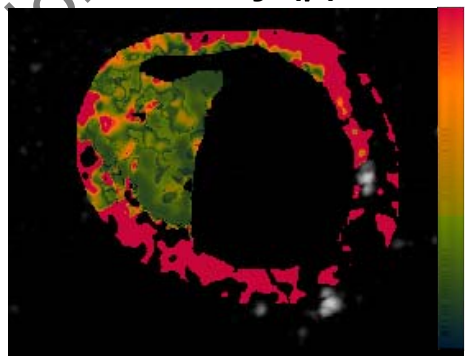
Scalability to All Pre-clinical Models



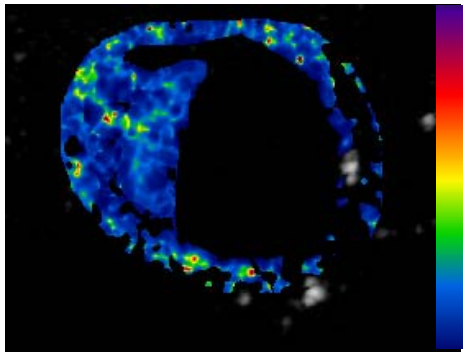
MBV



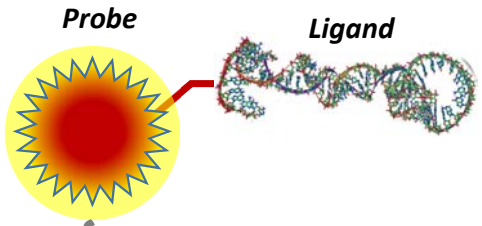
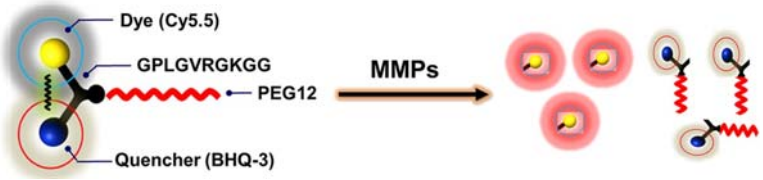
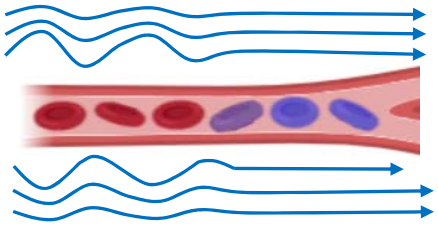
Velocity (β)



GOF



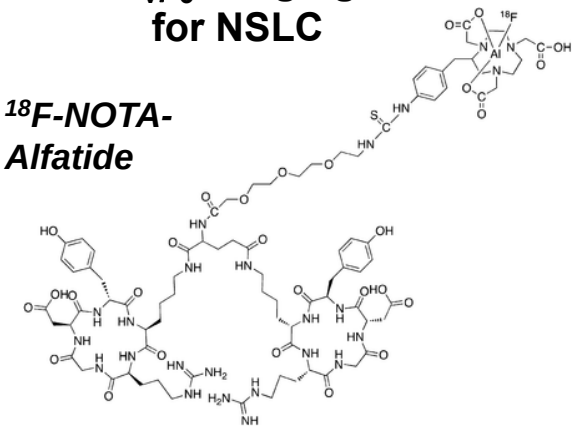
Strategies for Molecular Imaging

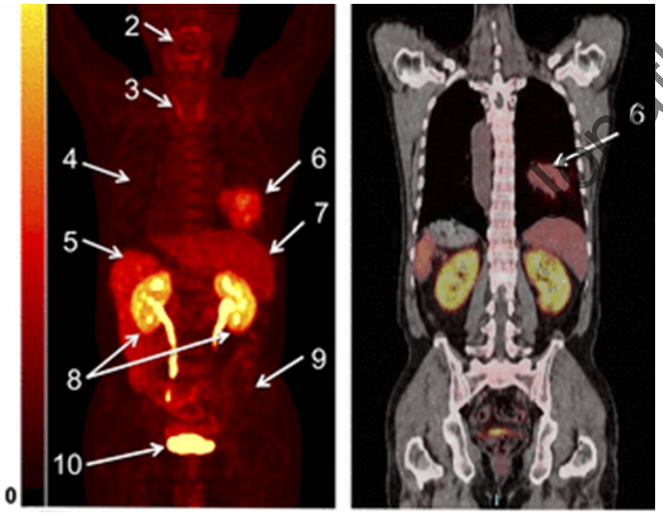
Ligand-receptor binding for tracer retention or altered kinetics	
Cellular retention from metabolic process	 Sohoni S, Cancer Res 2019;79:2511
Tracer activation by targeted metabolic or enzymatic process	 Chang D, Sci Rep 2015;19:16951
Endogenous signal characteristics without contrast agent	 **BOLD**

Molecular Imaging of NSLC

$\alpha_v\beta_3$ Imaging for NSLC

^{18}F-NOTA-Alfatide

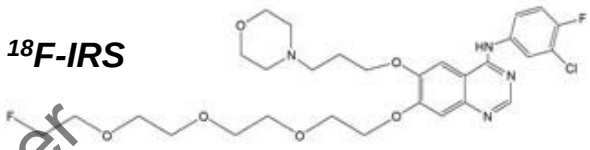


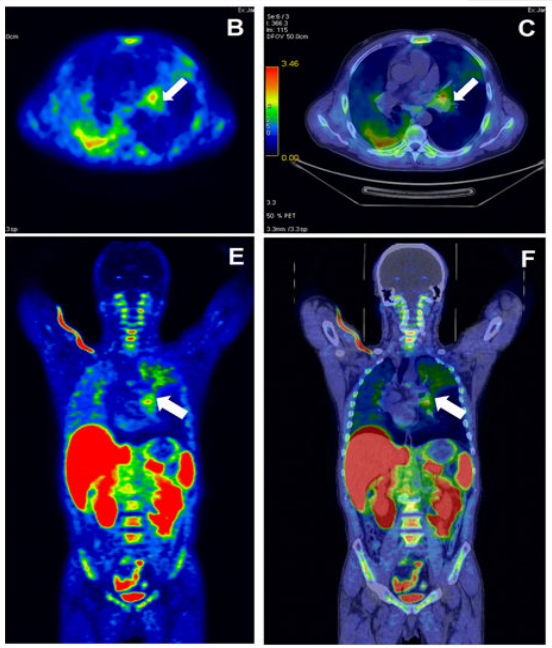


Wan L et al. J Nucl Med, 2013; 54(5):691-8

Mutant EGFR Imaging for NSCLC

^{18}F-IRS





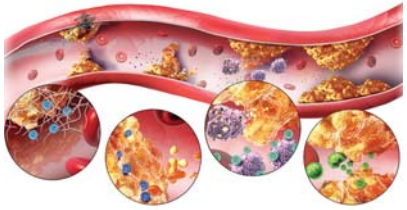
Song Y, et al. Sci Reports, 2017;7:3121

Role Pre-clinical and Clinical Molecular Imaging

Basic Research & Discovery 	Pre-clinical & Clinical Research 	Clinical Medicine 
Uncovering pathophysiology	Rapid evaluation of new therapies	Early diagnosis
Phenotyping animal models of disease	Optimization of therapies	More definitive diagnosis
Matching molecular process to anatomy or function	Evaluating mechanism of therapy or off target effects	Evaluating response to therapy
Matching gene expression to molecular or anatomic phenotype	Tracking cell or gene therapy	Precision therapy
	Understanding resistance to disease	Monitoring disease progression or prognosis

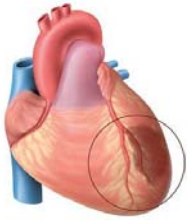
Molecular Imaging in Cardiovascular Medicine

Atherosclerosis



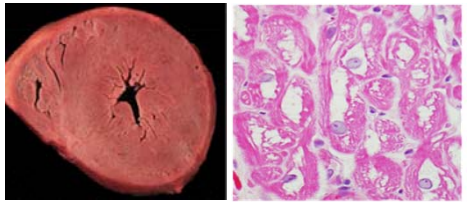
Inflammation Oxidation
Plts/VWF Angiogen.
Proteases TF, fibrin

Ischemia



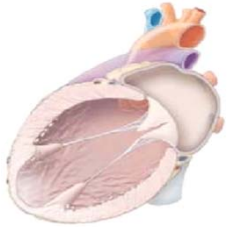
Hypoxic metabol.
Inflammation
HIF1-activation

Infiltrative CM



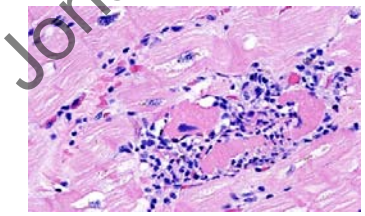
Amyloid β CD-16
Thioflavin UT Lysosome
ApoE4 Autophagy

Remodeling



MMPs/TIMPs
GF & Integrins
Inflammation
RAAS Rec/Transcript

Myocarditis & OHT Rejection



ECAMs
Chemokines
Inflammatory cells
Apoptosis/Caspases

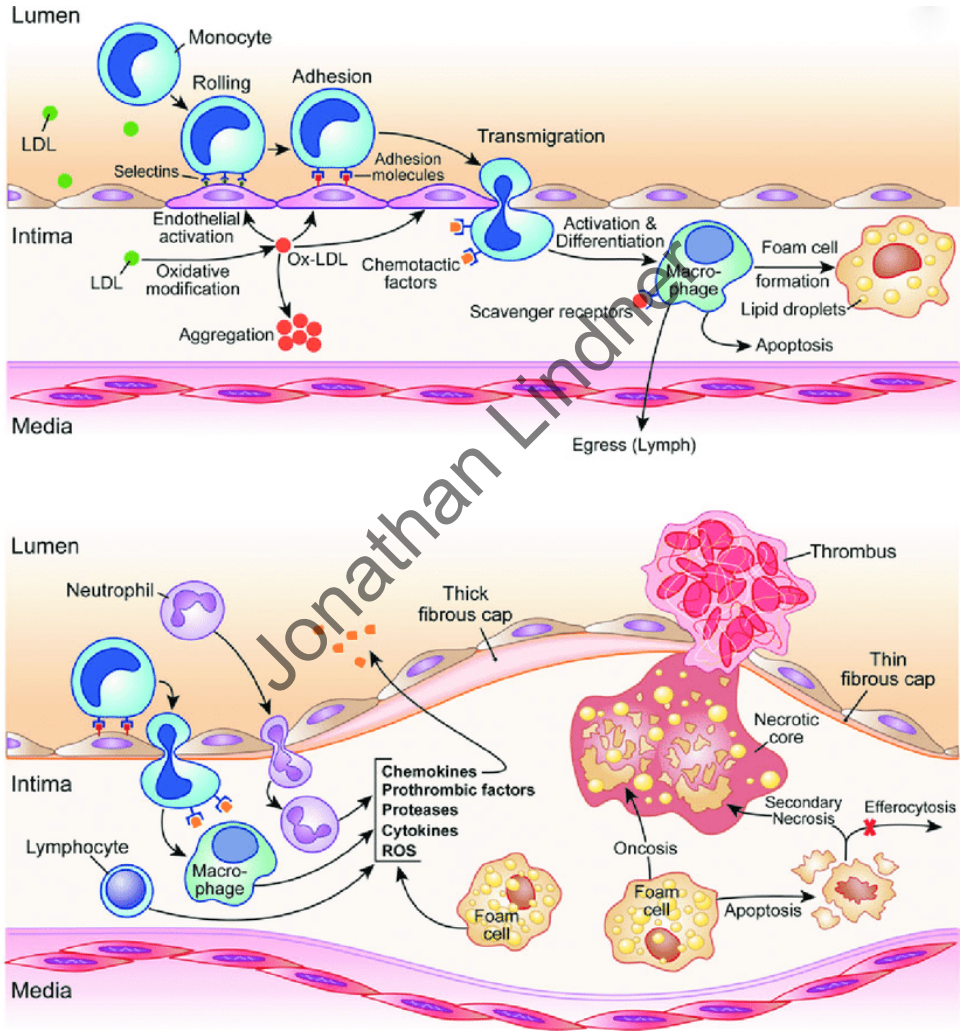
Arrhythmogenesis

Cell junction proteins
Matrix remodeling
Channel density/activity
Sympathetic activity

Classical Pathway of Atherogenesis

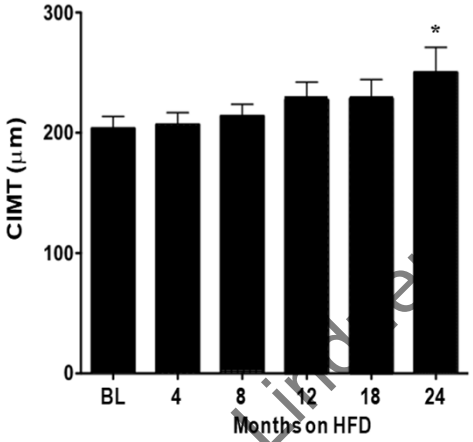
Early

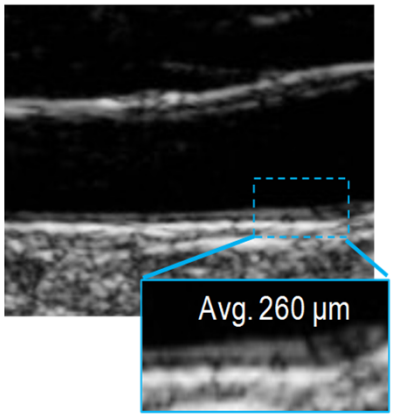
Advanced

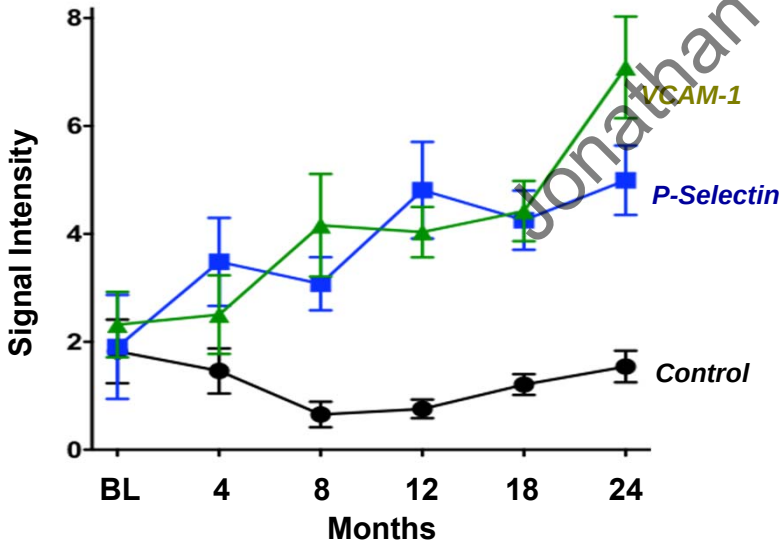


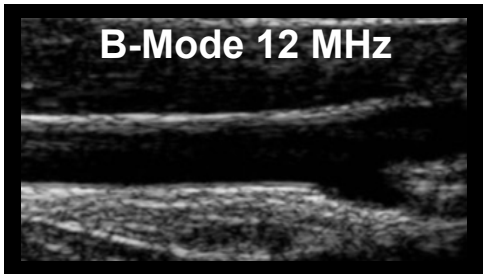
Tavakoli S, et al
Antioxid Redox Sign
2012;17:1785

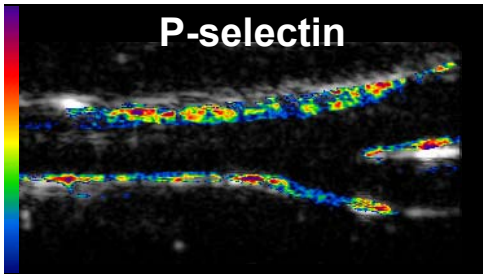
Endothelial Phenotype in Diet-induced Obesity







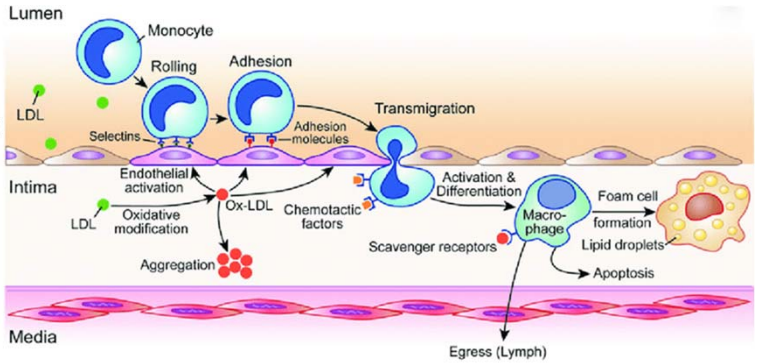




Chadderdon S, et al.,
Circulation 2014;129:471

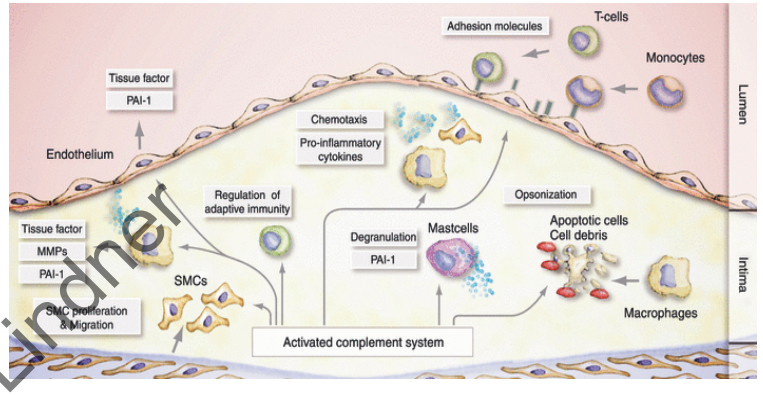
Contemporary Concepts in Atherosclerosis

Classical Inflammatory Pathway



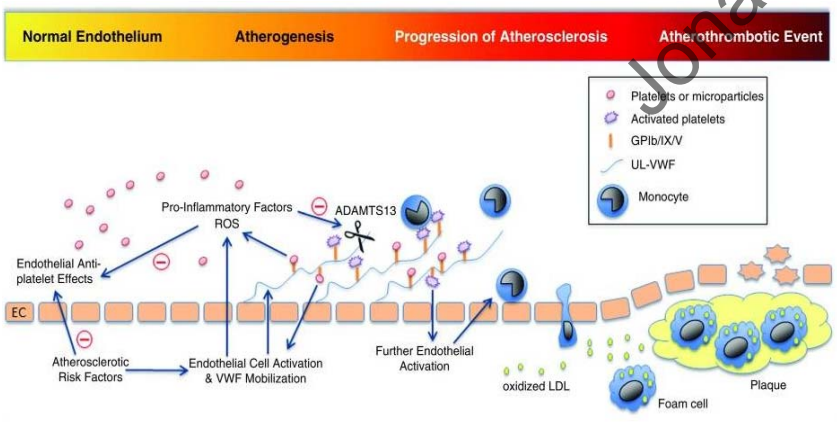
Tavakoli S, et al. Antioxid Redox Sign 2012;17:1785

Complement Pathways



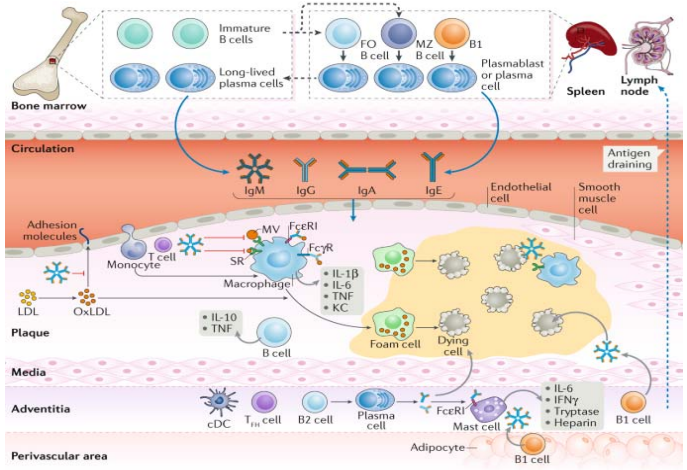
Speidl WS, et al. J Thromb Hemast 2010;9:428

VWF-mediated Platelet Adhesion



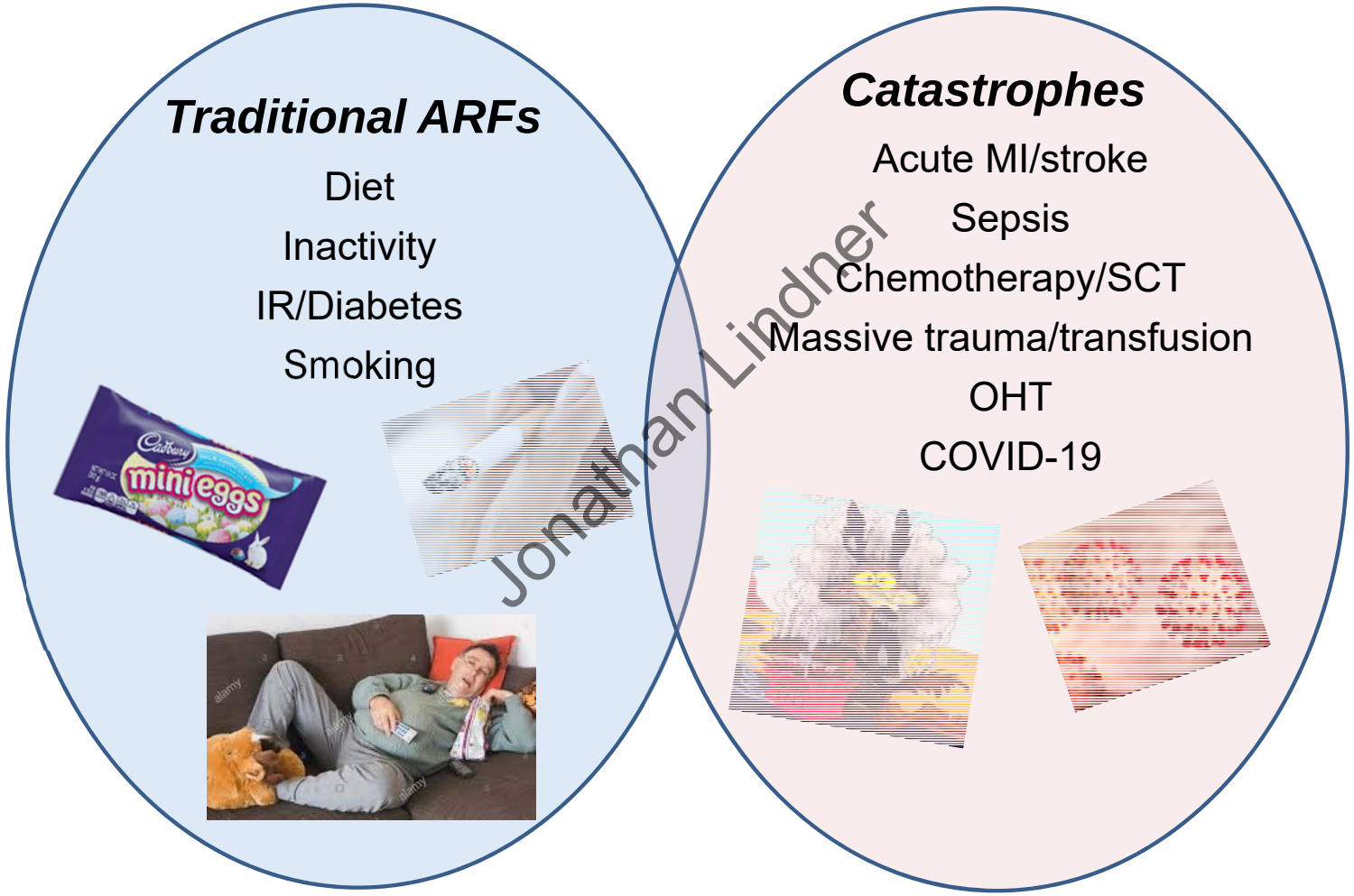
Wu M, et al., Blood 2017;129:1415

Adaptive Immune Response

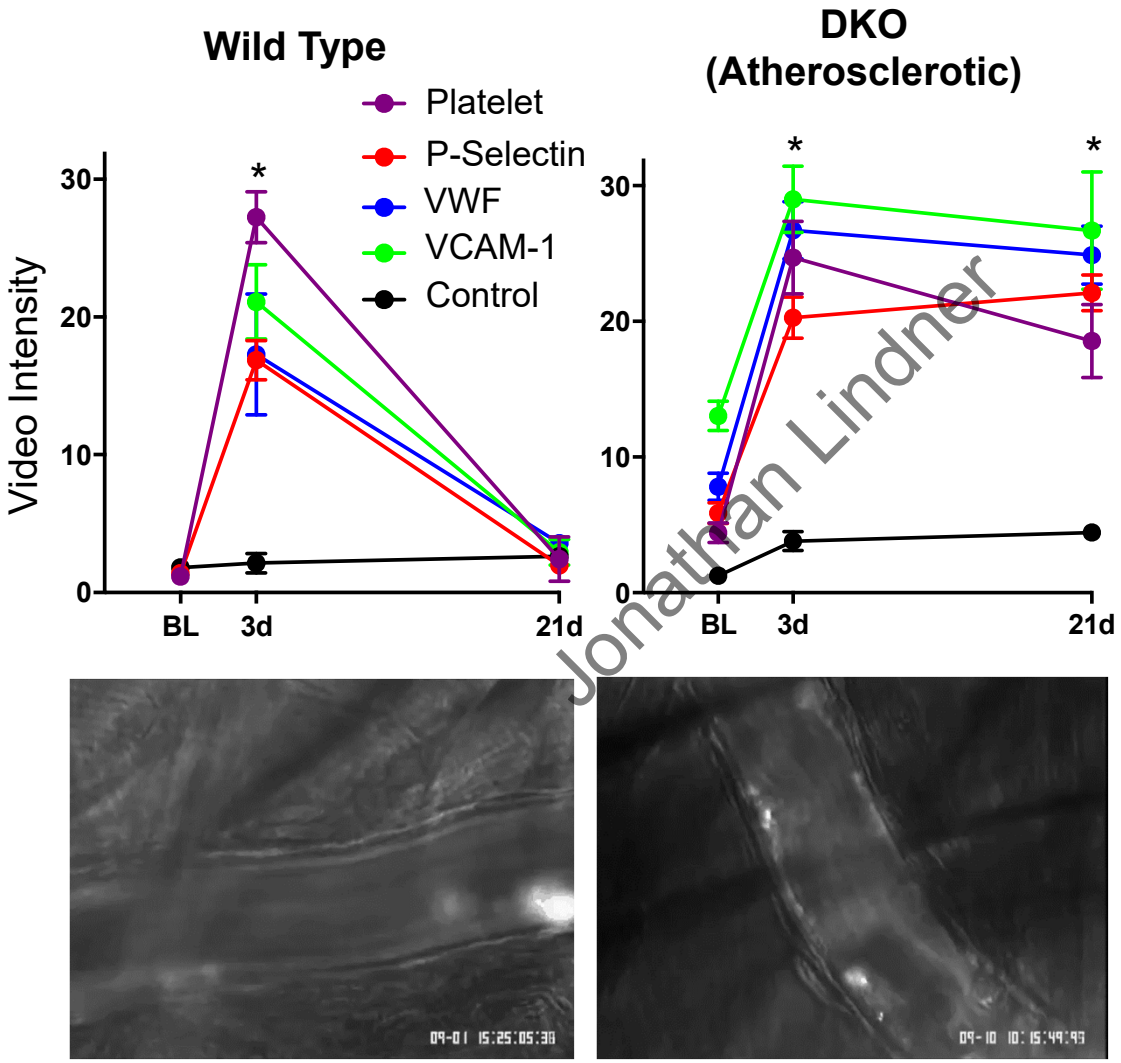


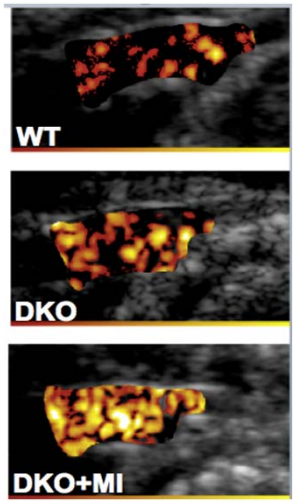
Sage AP, et al., Nat Rev Cardiol 2019;16:180

The Athero-accelerating Triggers



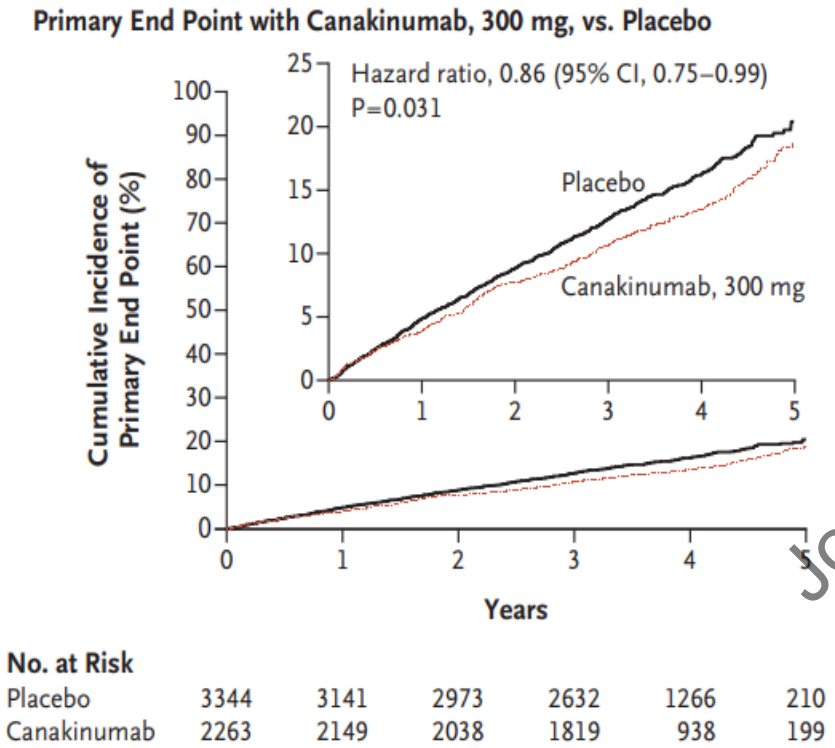
Remote Plaque Activation

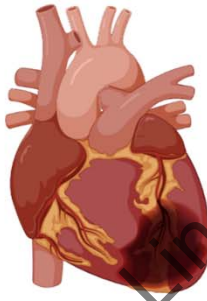


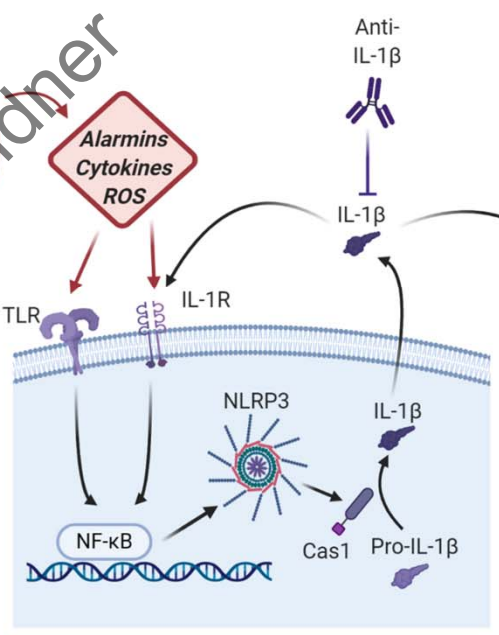


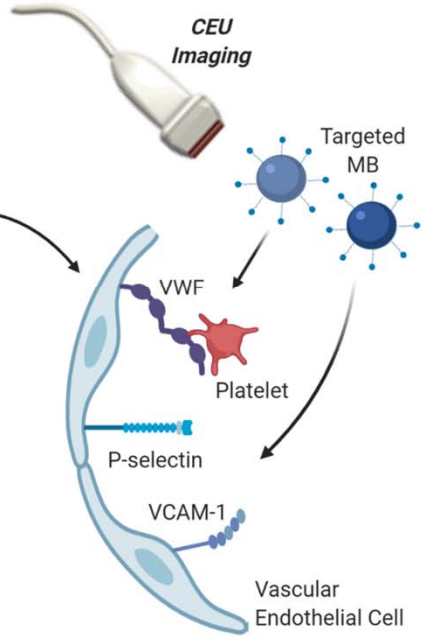
Moccetti F, et al.,
JACC 2018;72:1015

CANTOS: Effects of IL1β Inhibition





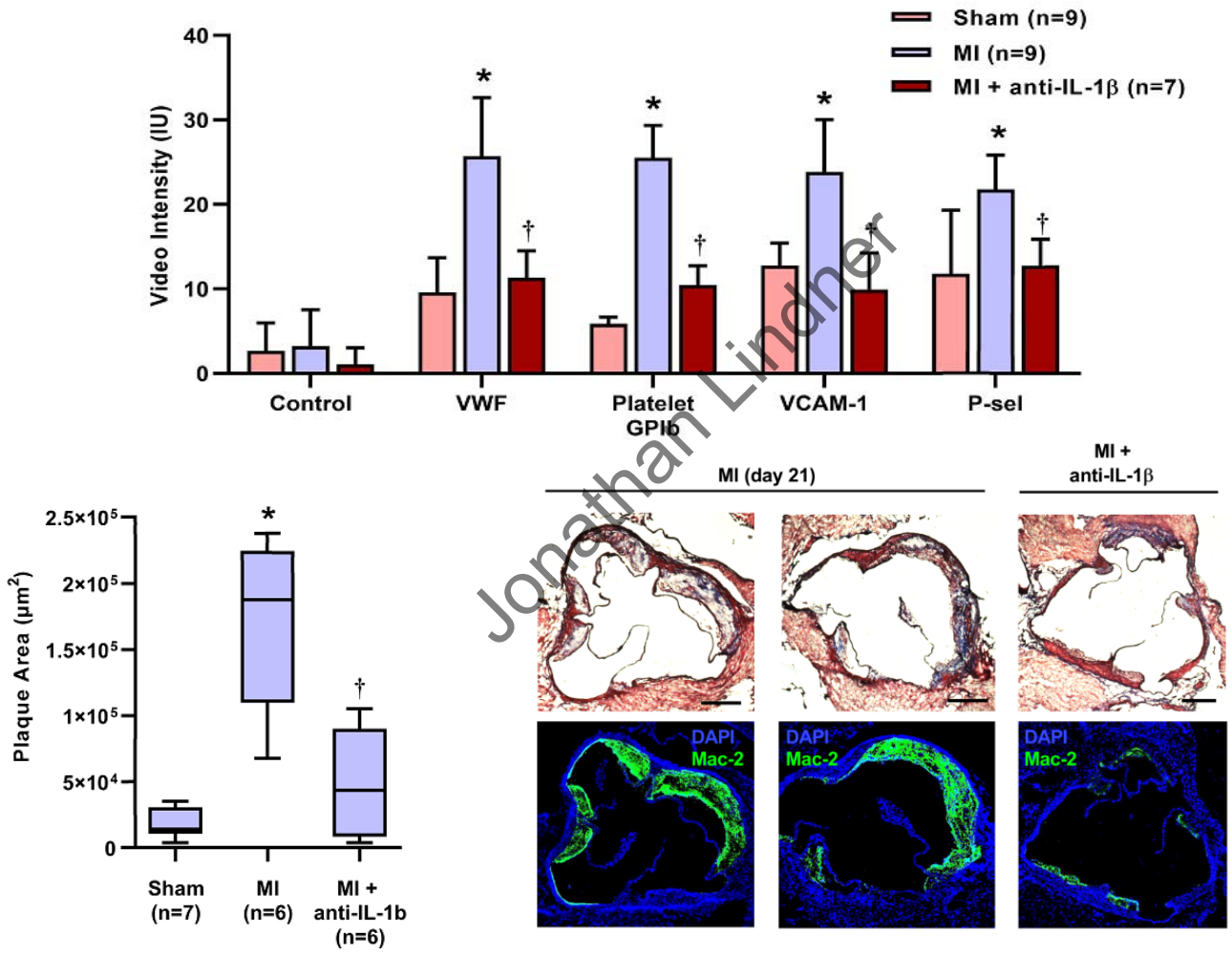




Ridker PM, et al. NEJM 2017;377:1119

Shentu W, et al. JASE 2021;34:433

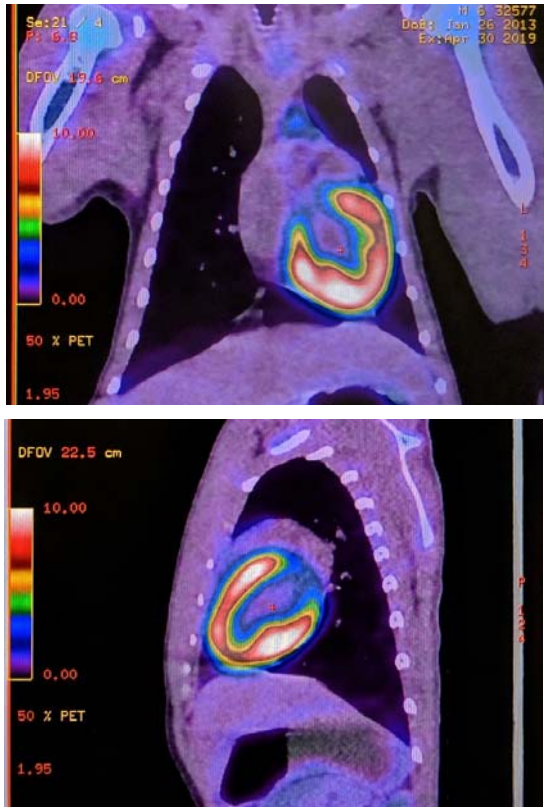
Remote Plaque Activation: Effect of IL1β-inhibition



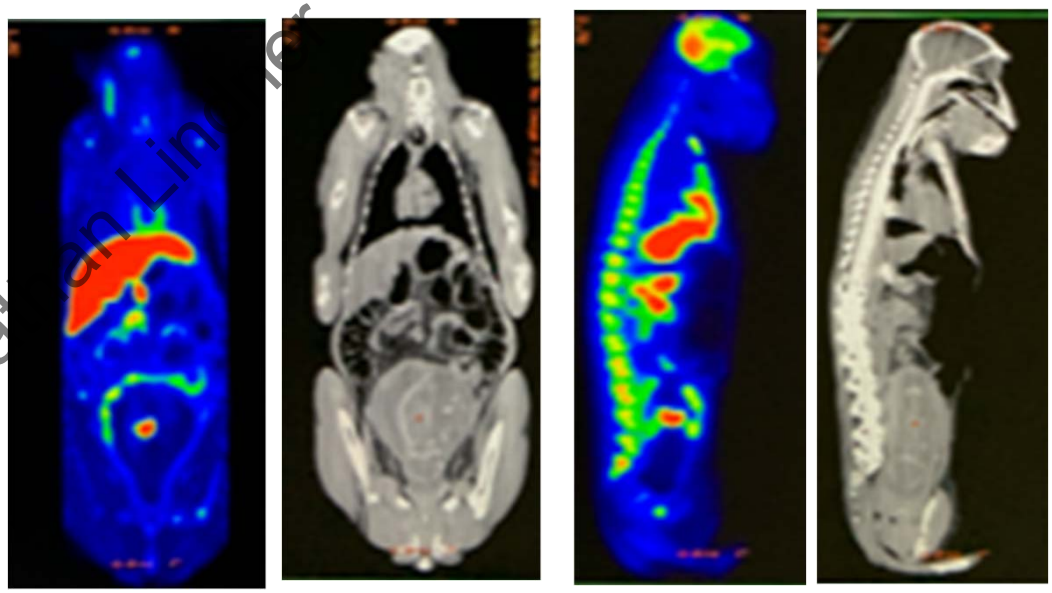
Shentu W, et al.
J Am Soc Echocardiogr
2021;34:433

Molecular Imaging of Metabolism and HDAC

^{18}F-FDG PET



^{11}C-HDAC PET



Conclusion