THE GEORGE WASHINGTON UNIVERSITY

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From Animal Models to Human Physiology

Mathematical Modeling in Physiology: Biomedical Applications

Moscow, March 21-24, 2016

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The Alisann and Terry Collins Professor & Chairman, Department of Biomedical Engineering

Mathematical Modeling in Physiology

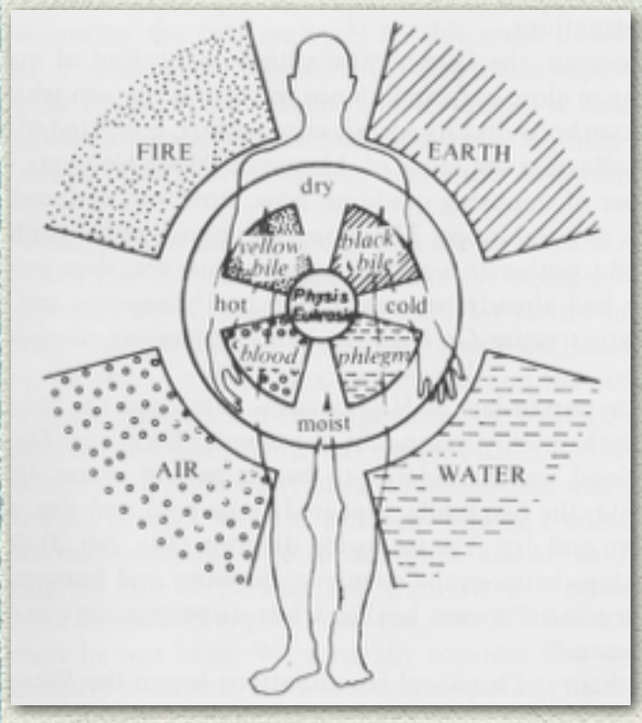
Ivan Pavlov, portrait by Mikhail Nesterov

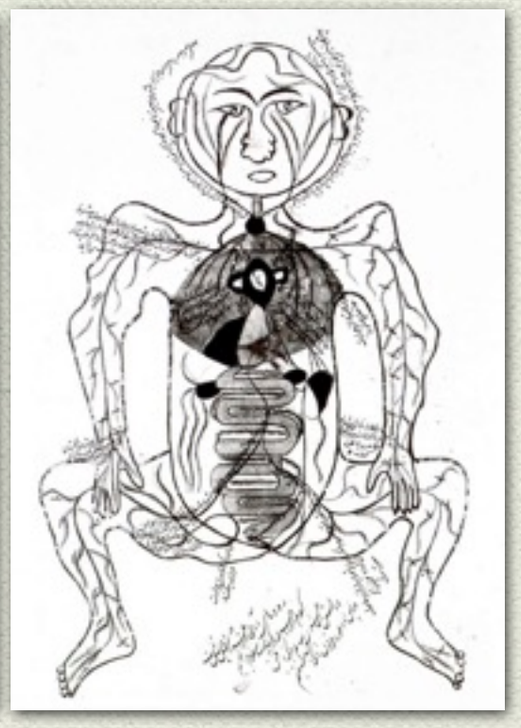
Ivan Pavlov, "Natural Science of the Brain", Moscow 1909:

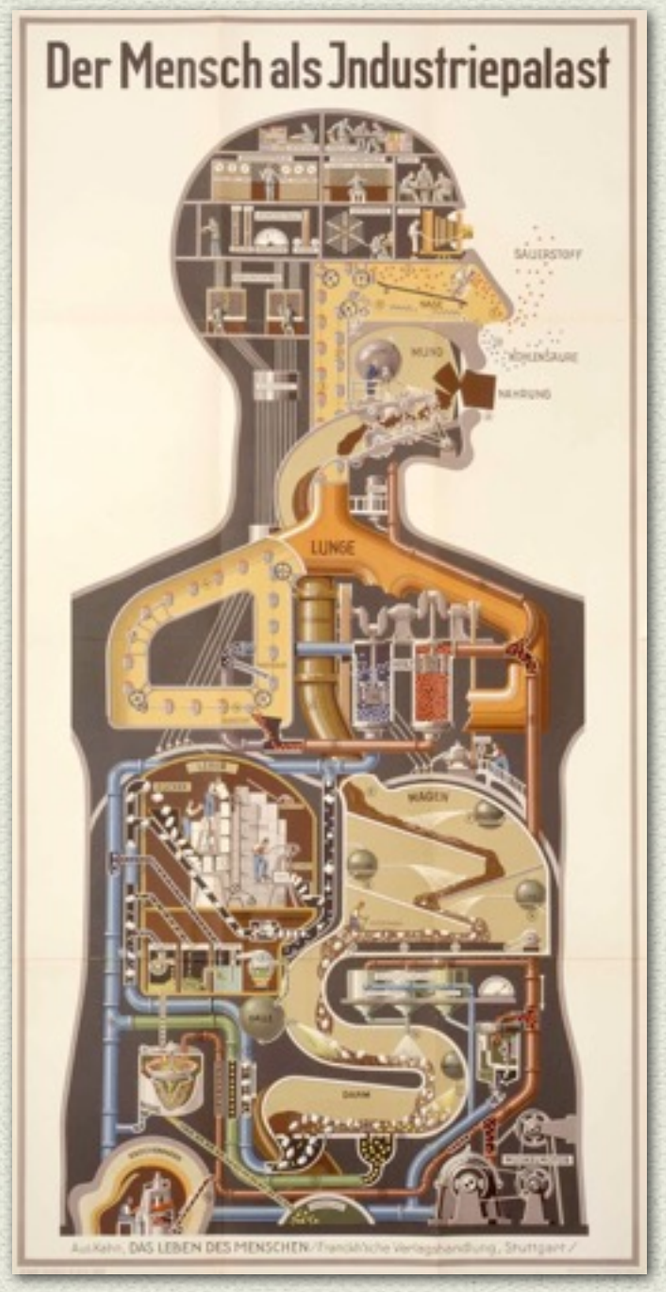
"As a part of nature, every animal organism represents a very complicated, closed system, the internal forces of which, at any given moment, as long as it exists as such, are at the equilibrium with the external forces of its environment... The time will come, be it ever so distant, when mathematical analysis, based on natural science, will include in majestic formulae all these equilibrations and, finally, itself"

Babkin B.P., Pavlov: A Biography. The University of Chicago Press, Chicago and London, 1946, p. 85.

Prevailing Thought Style in Physiology



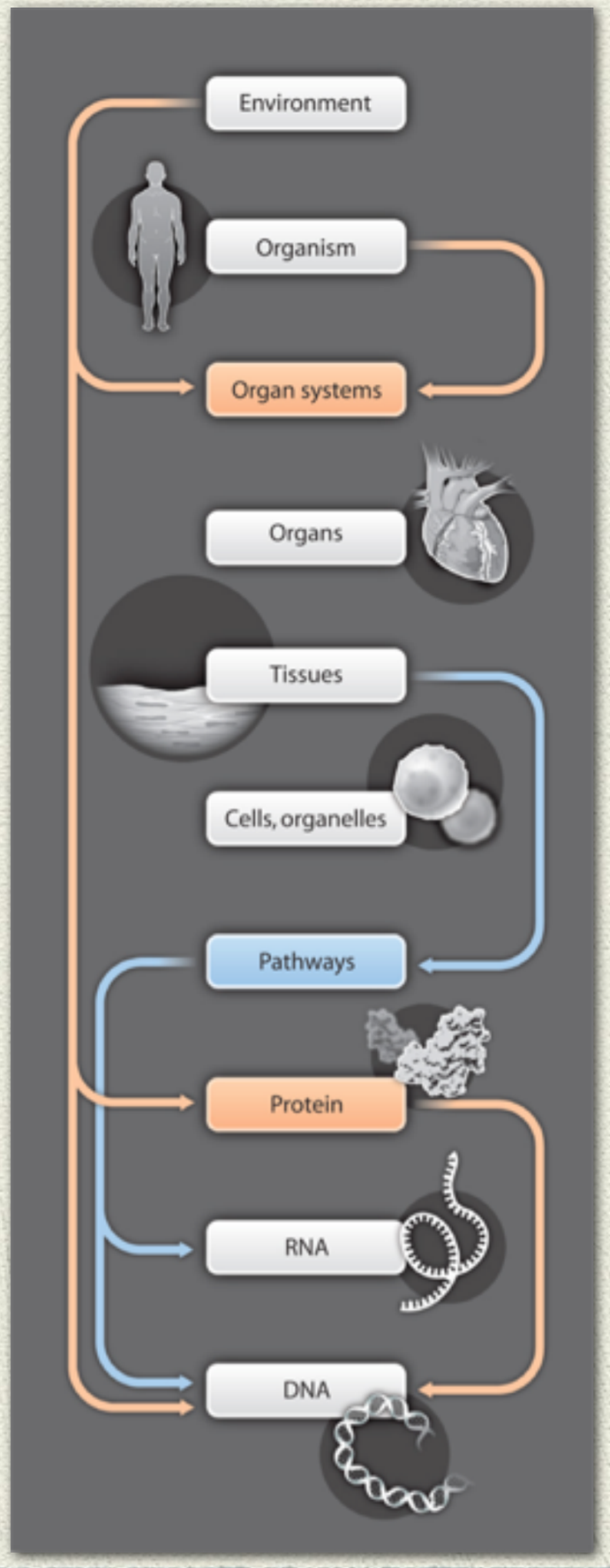


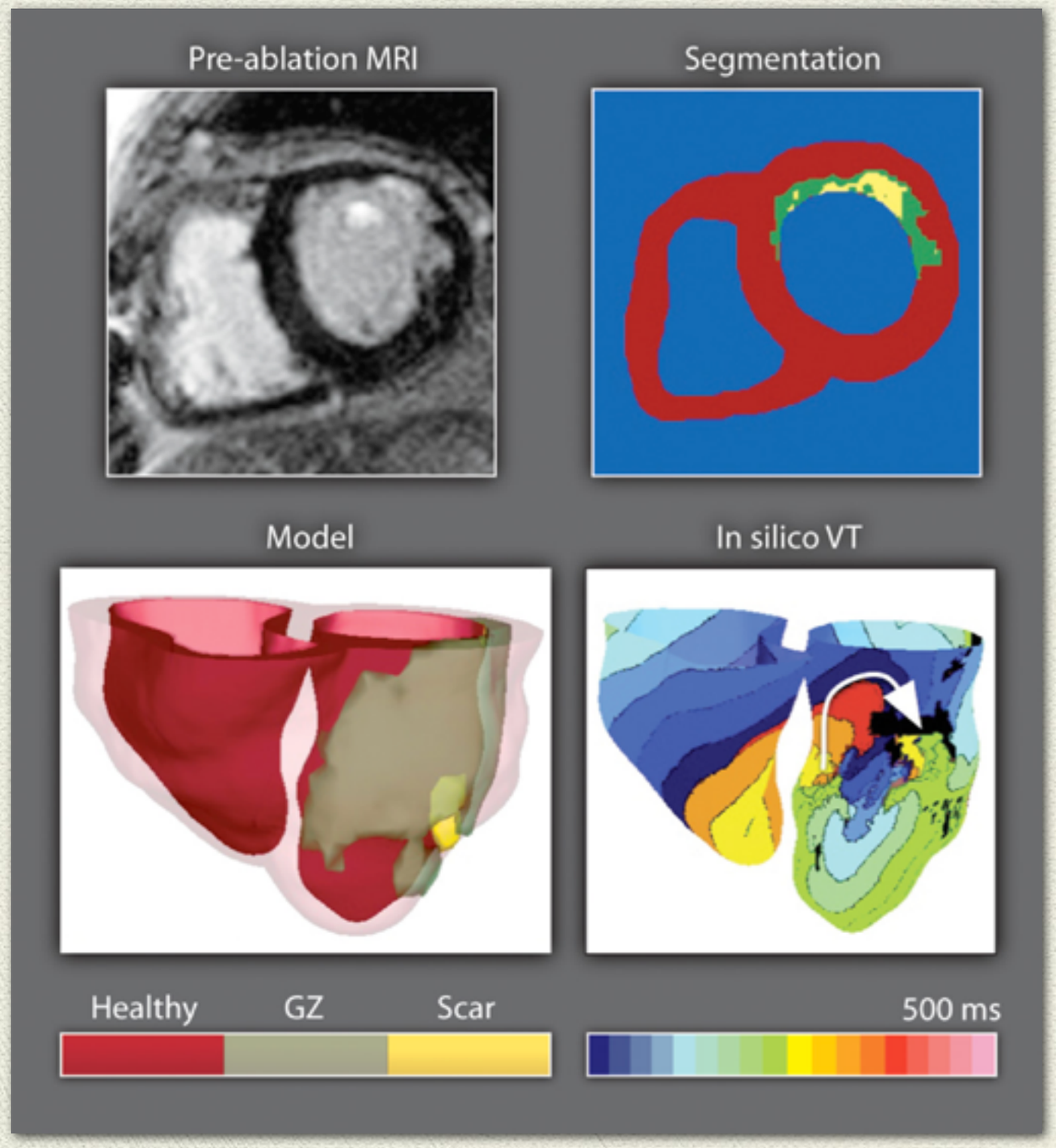


"The explanation given to any relation can survive and develop within a given society only if this explanation is stylized in conformity with the prevailing thought style"

Ludwik Fleck, Genesis and development of a scientific fact. 1935/1979.

Multiscale Modeling





Winslow et al, 2012

Outline

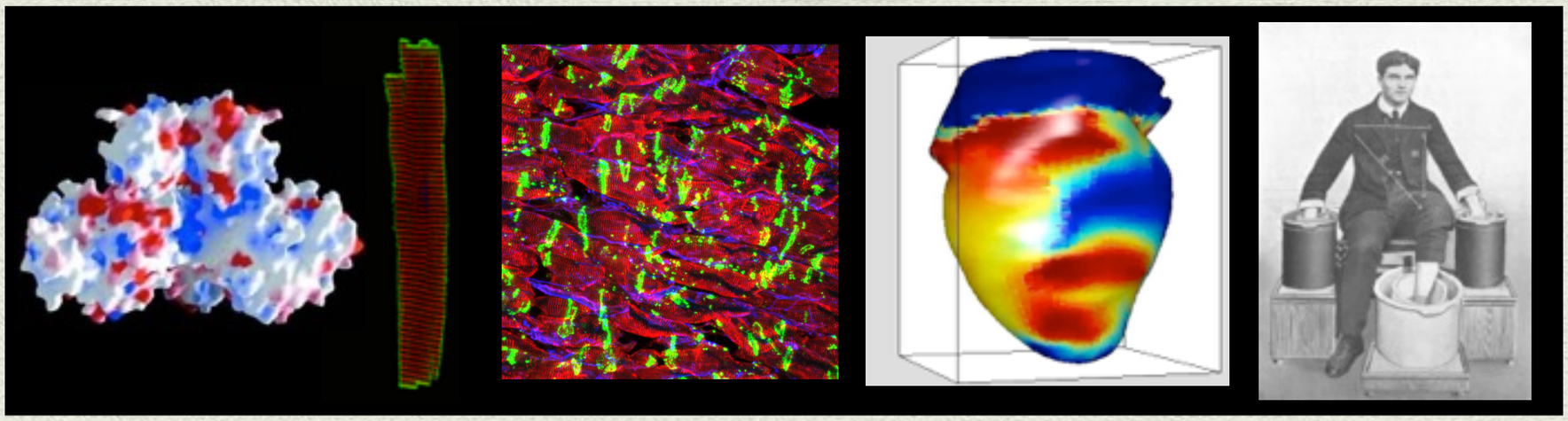
- Need for quantitative human physiology
- Electrophysiology remodeling
- Metabolic remodeling
- Adrenergic remodeling
- New methodology

Early history of resuscitation

XVIII-century resuscitation by blowing smoke into the rectum and applying electrical stimulation to the chest.
Courtesy of Wood Library-Museum of Anesthesiology, Park Ridge, Illinois.

Translational Research Paradigm

integration



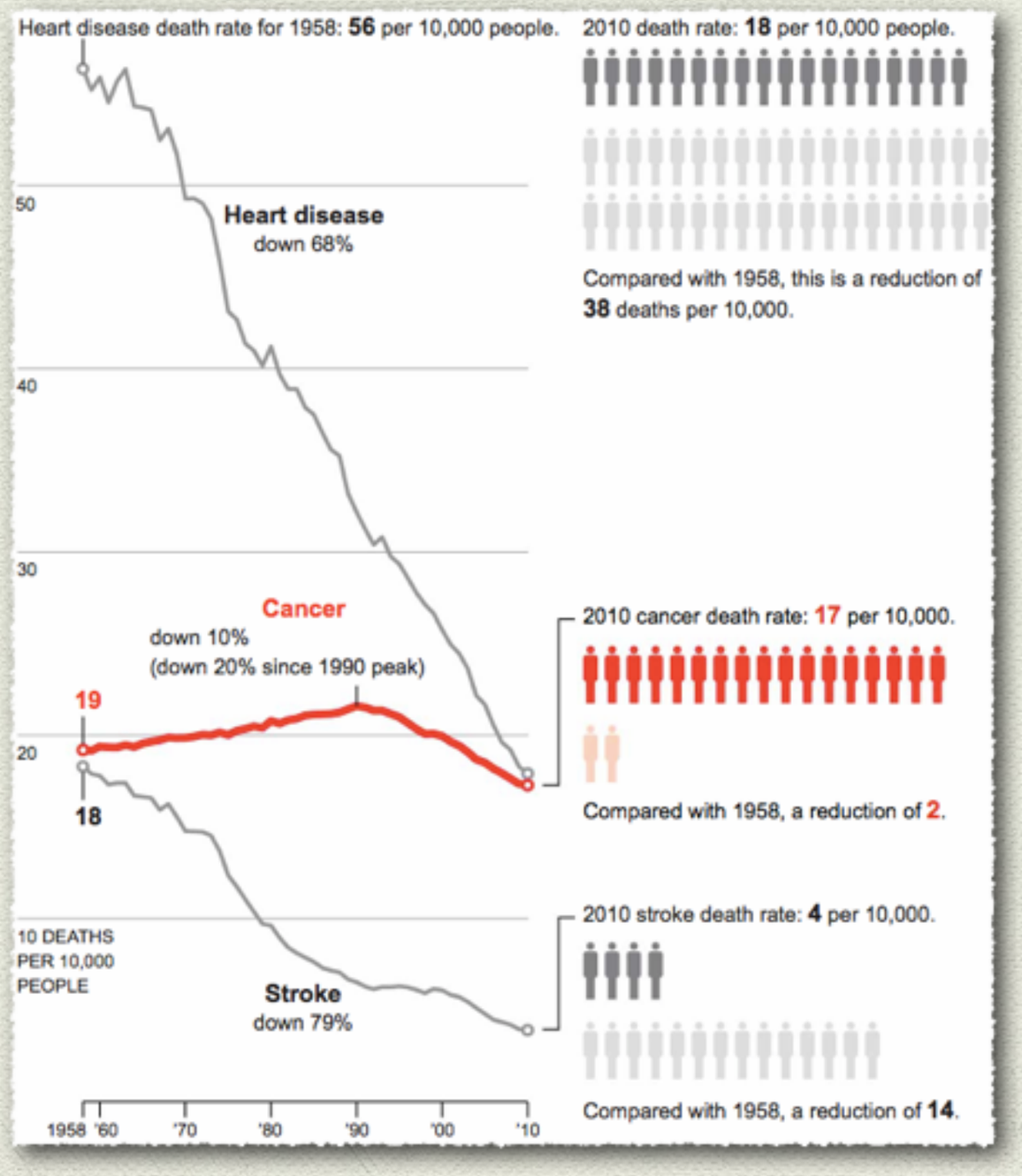
reduction

- Identifying the clinical determinants of the disease at bedside
- Reproducing the symptoms of the disease in an animal model and identifying a potential therapy in this model
- Evaluating the safety and efficacy of the therapy in clinical trails

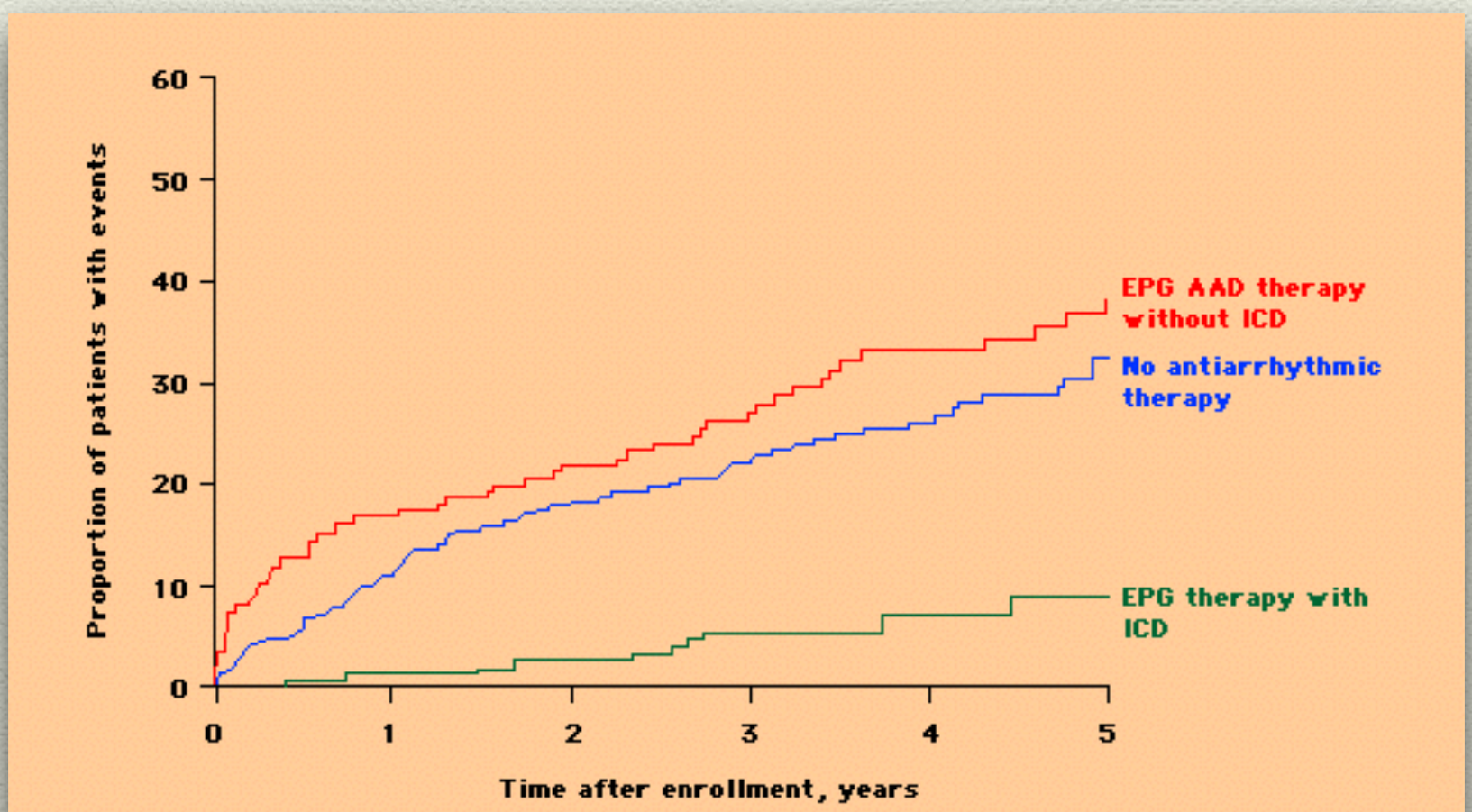
Result of Biomedical Research:
The Rise of US Life Expectancy (1958-2010)

- **The Rise in Life Expectancy**

- Black women 12.2 years
- White women 7.4 years
- Black men 10.8 years
- White men 9.1 years

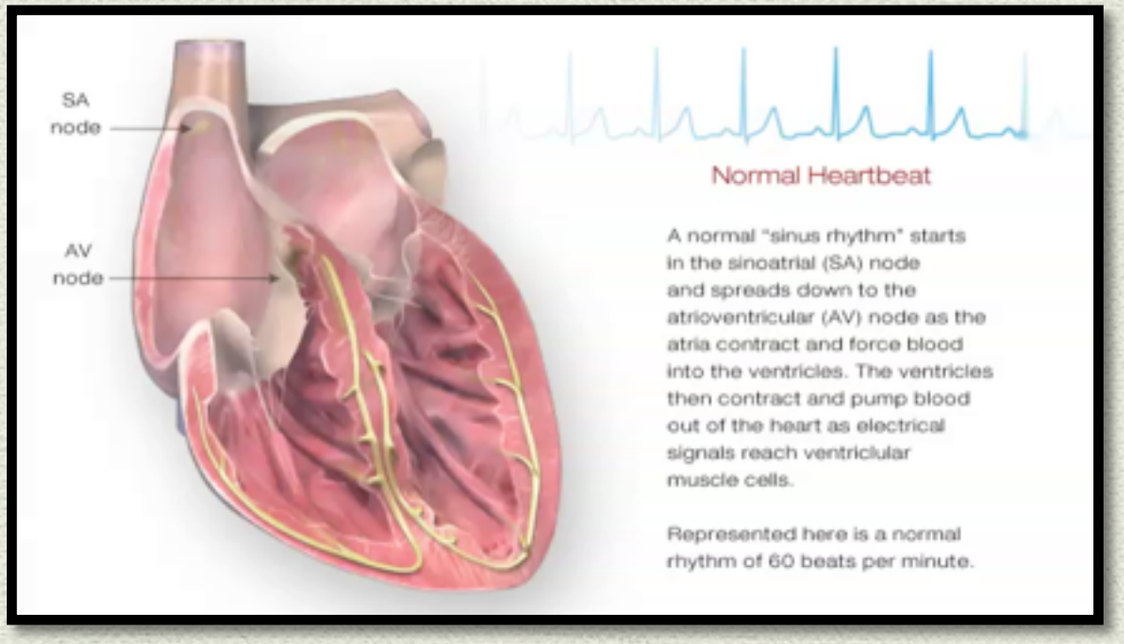


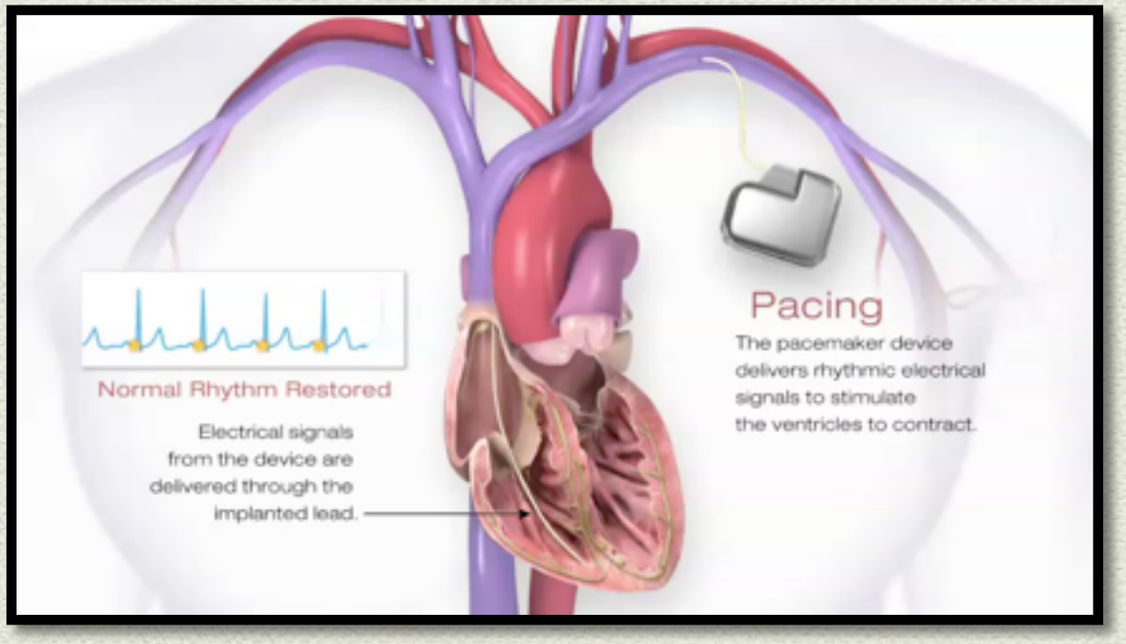
Failure of Anti-Arrhythmic Drug Therapy:
Electrophysiologically Guided AAD Therapy vs. ICD



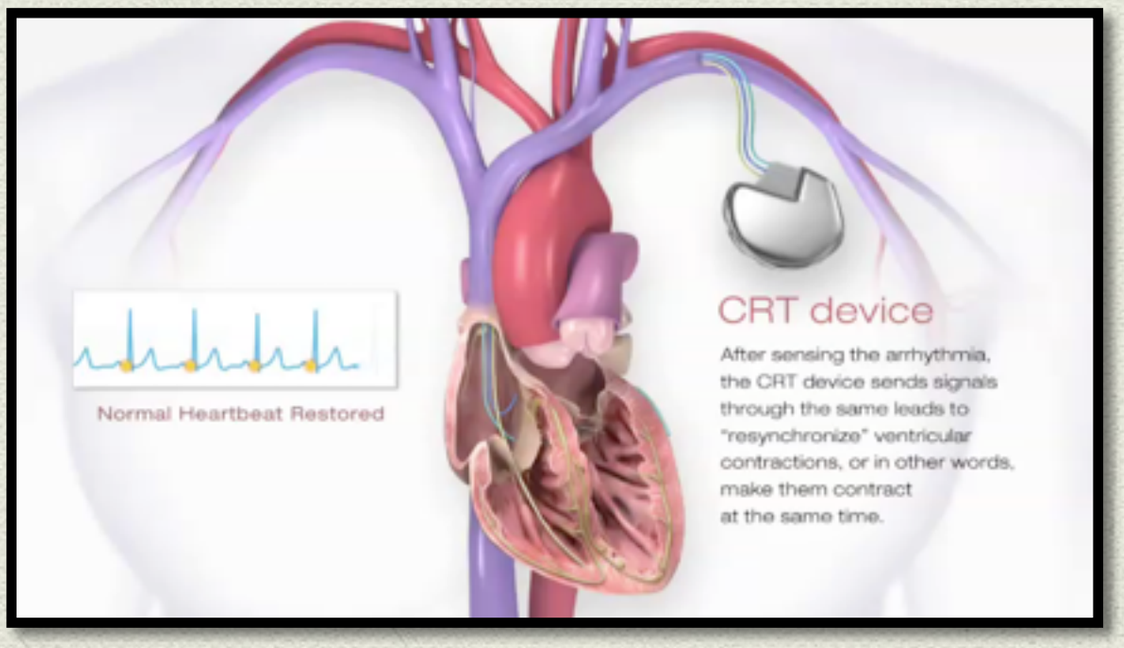
ICD reduces sudden death in MUSTT The MUSTT trial enrolled 704 patients with coronary artery disease, nonsustained ventricular tachycardia (VT) and a left ventricular ejection fraction ≤40 percent who had sustained VT induced during electrophysiologic (EP) study. Kaplan-Meier estimates show that the incidence of cardiac arrest or death from arrhythmia is significantly lower in those receiving an implantable cardioverter-defibrillator (ICD) compared to those receiving no therapy or those with EP-guided (EPG) antiarrhythmic drug (AAD) therapy. (Data from Buxton, AE, Lee, KL, Fisher, JD, et al, N Engl J Med 1999; 341:1882).

Bradycardia and Resynchronization

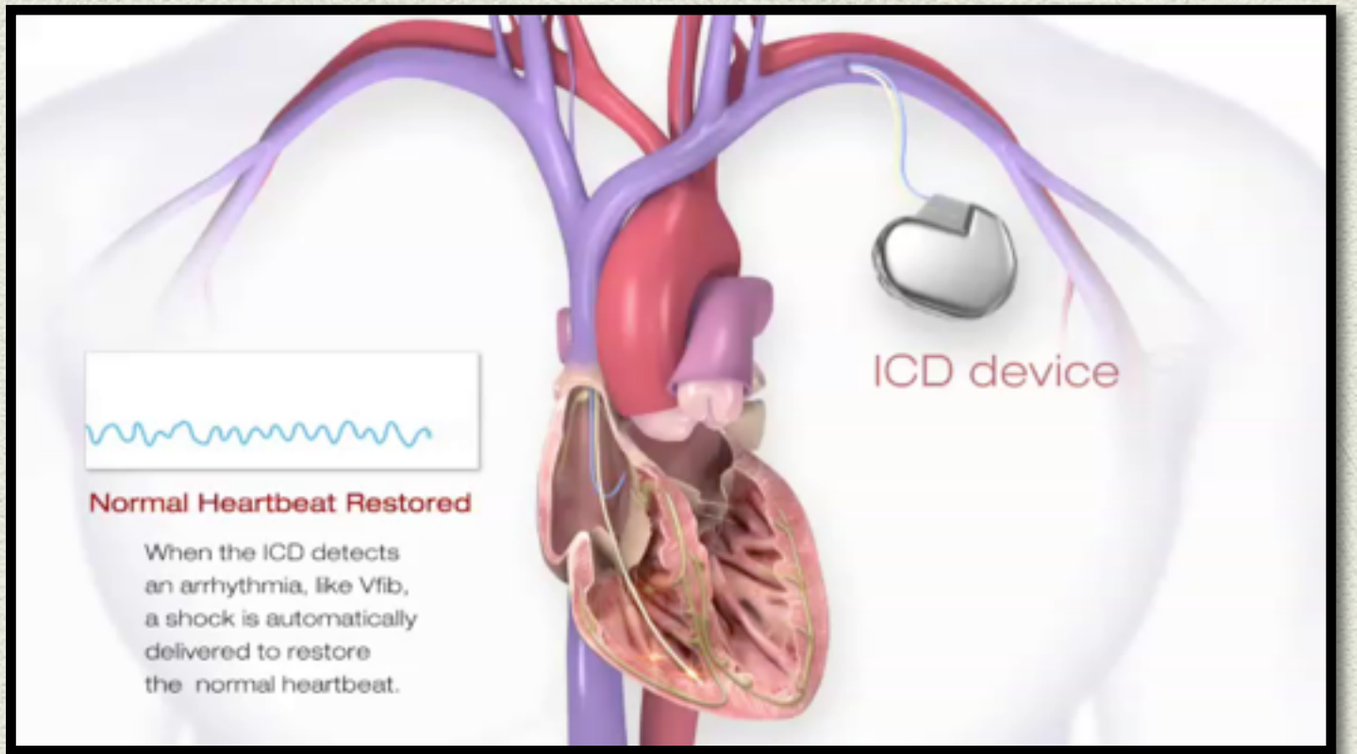


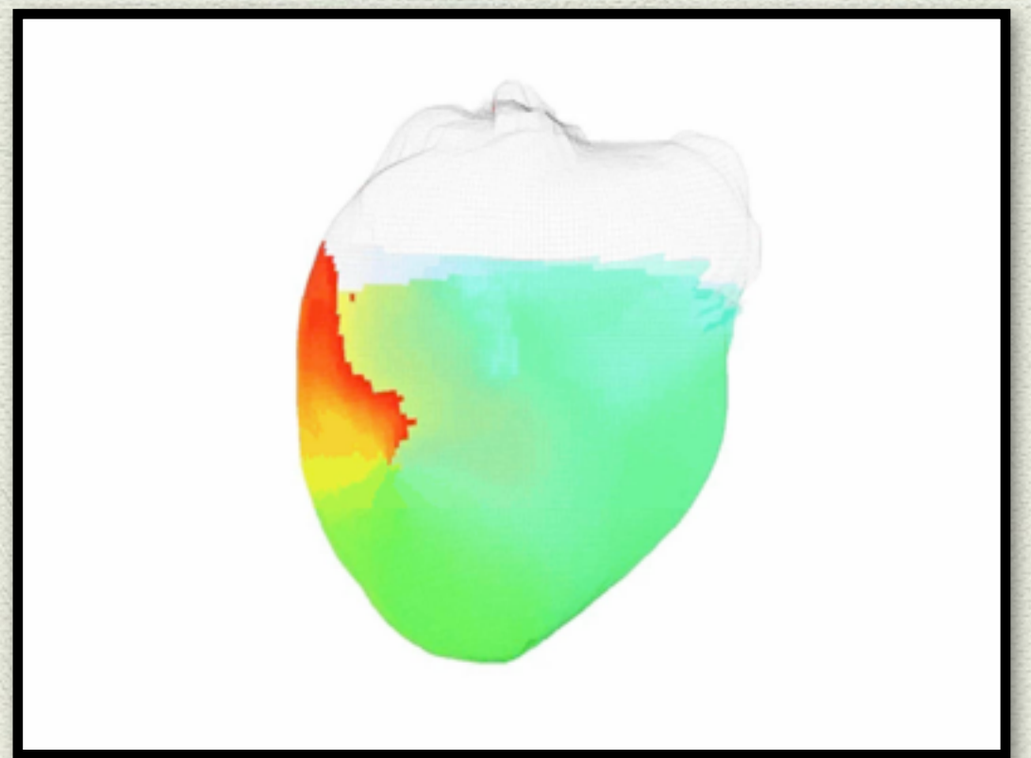


- Drug therapy: none
- Pacemakers: low-definition
- Device failure



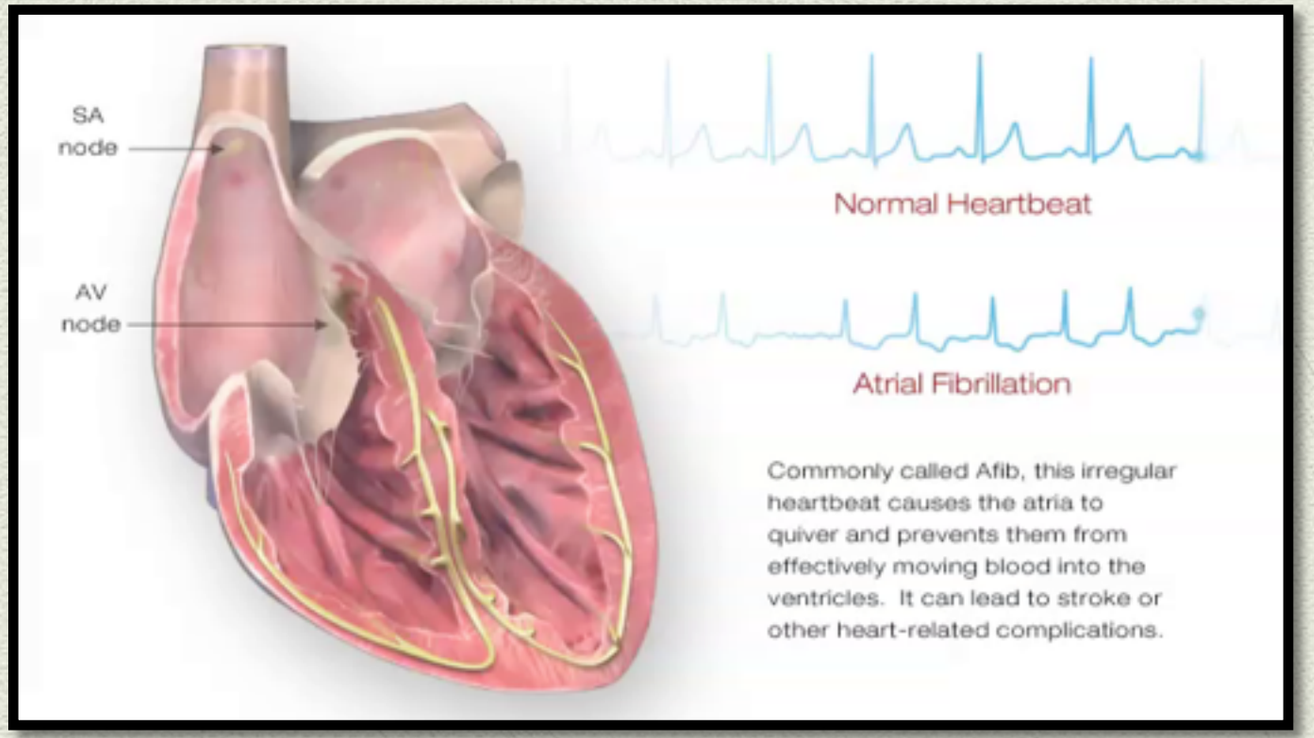
Ventricular Fibrillation: 400,000 Sudden Deaths per Year (US)

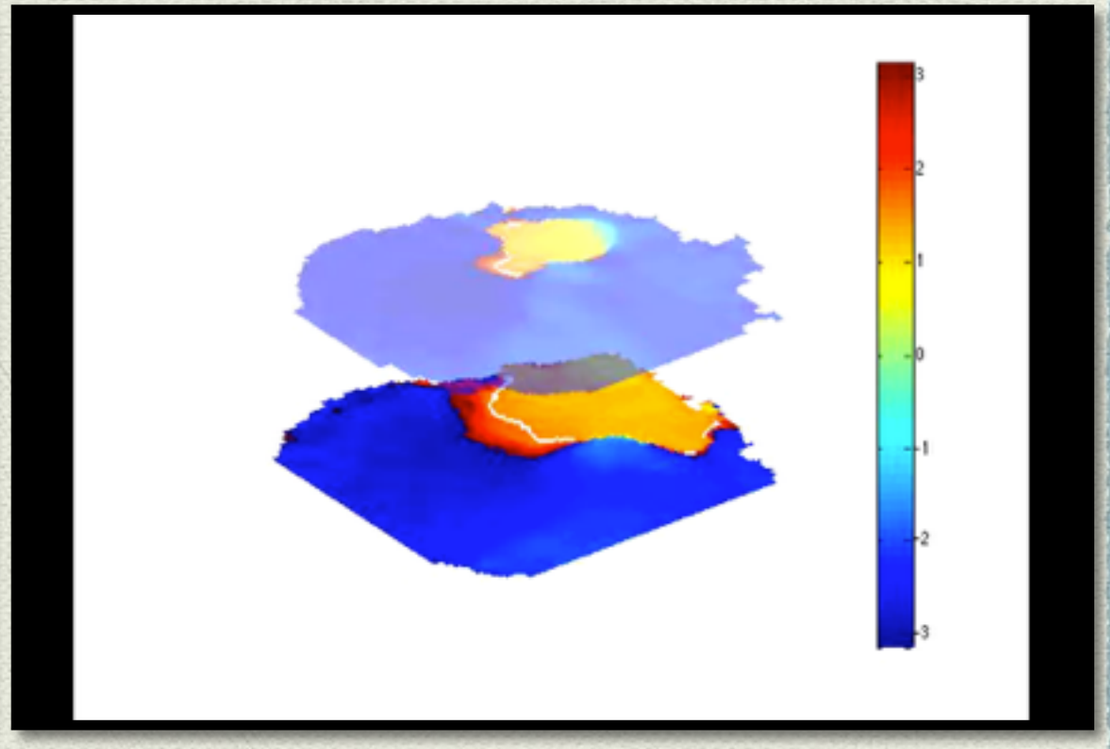




- Antiarrhythmic drugs: limited options
- Ablation: in progress of development
- Implantable defibrillator therapy: effective but side effects

Atrial Fibrillation: will increase from 5M to 15M patients by 2050 (US)





American Heart Association. Learn and Live

- Antiarrhythmic drug therapy: efficacy 15% and side effects
- Ablation: high recurrence, less effective in persistent
- Implantable device therapy: none, too painful

Jessica Bolker. Model organisms: There's more to life than rats and flies. Nature 491, 31–33, 2012

- "... Many careers, labs and journals are built on the primacy of the fly, mouse and worm"
- "But studying only a few organisms limits science to the answers that those organisms can provide"
- "Disparities between mice and humans may help to explain why the millions of dollars spent on basic research have yielded frustratingly few clinical advances"

Tiny impact of "wet bench" advances on human health

Jeff Robbins (Circ. Res., 2011): "What have we learned in the past 20 years? Although the pace of data acquisition and subsequent definition of multiple signaling pathways, gene function, and normal and pathogenic mechanisms has been exhilarating, we cannot help but be humbled by the relatively tiny impact of these data on human health in general and cardiovascular disease specifically. Our "wet bench" advances have not, with rare exceptions, been translated to the bedside. Although this failure is due at least in part to our inability to effectively apply what we have learned to drug development, it also reflects remaining, serious deficits in understanding the mechanisms that drive cell and organ function."

Opportunities for Human Heart Research: Organ Procurement Orgs

American Journal of Transplantation 2015; XX: 1–8
Wiley Periodicals Inc.

doi: 10.1111/ajt.13055

National Decline in Donor Heart Utilization With Regional Variability: 1995–2010

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[3]California Transplant Donor Network, Oakland, CA
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[5]Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC

criteria for donor heart evaluation and acceptance for transplantation.

Abbreviations: INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assis fraction; MPSC, Committee; OE, Procurement ar United Network

Received 31 Aug accepted for pub

American Journal of Transplantation 2014; 14: 615–620
Wiley Periodicals Inc.

doi: 10.1111/ajt.12607

A Novel Organ Donor Facility: A Decade of Experience With Liver Donors

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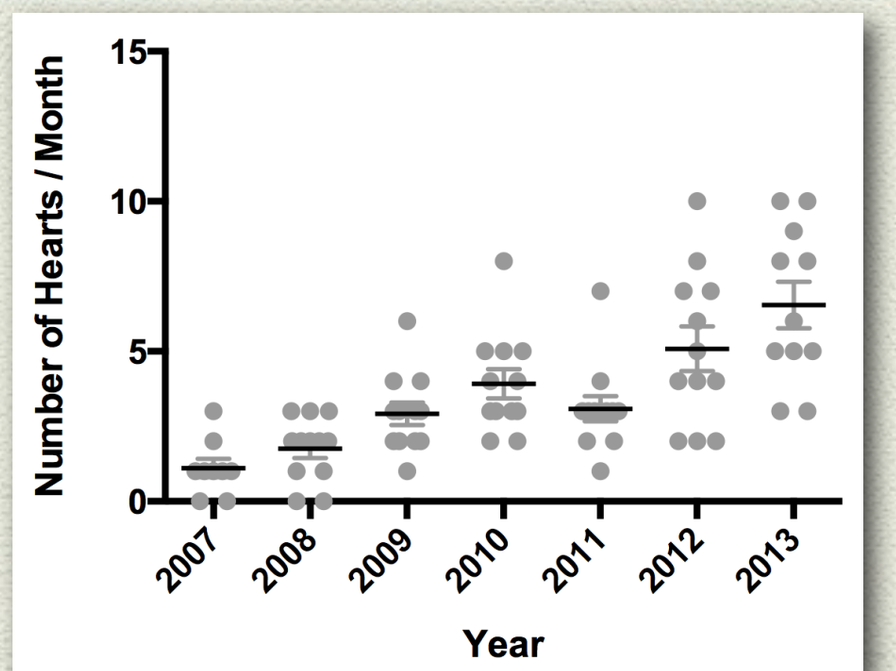
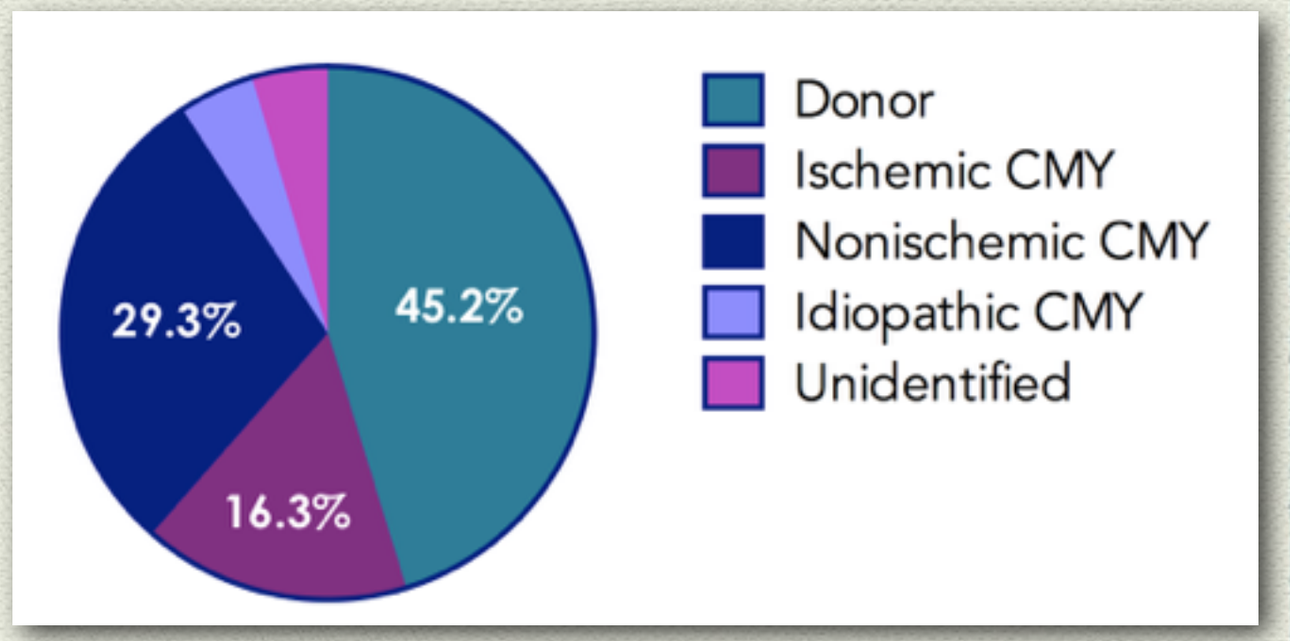
Introduction

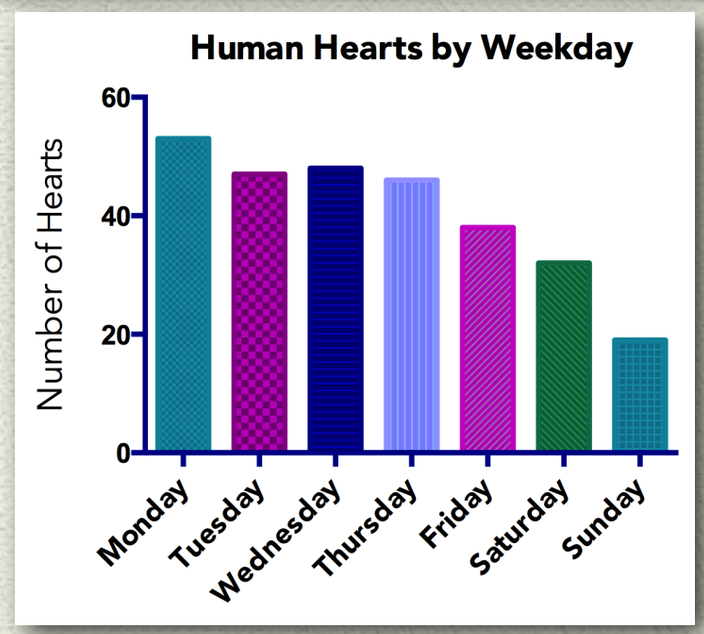
In the United States, the experience of donor procurement is often time consuming and logistically challenging for organ procurement organizations (OPOs) and organ recipient centers. Typically, transplant surgeons from the recipient center travel to the organ donor's hospital and perform complex, time-sensitive procedures with inexperienced staff in unfamiliar surroundings. Most donor recoveries require multiple teams to travel to the recovery hospital (1). On average, brain-dead donors lead to three solid organ transplants (US average) but may lead to as many as six or

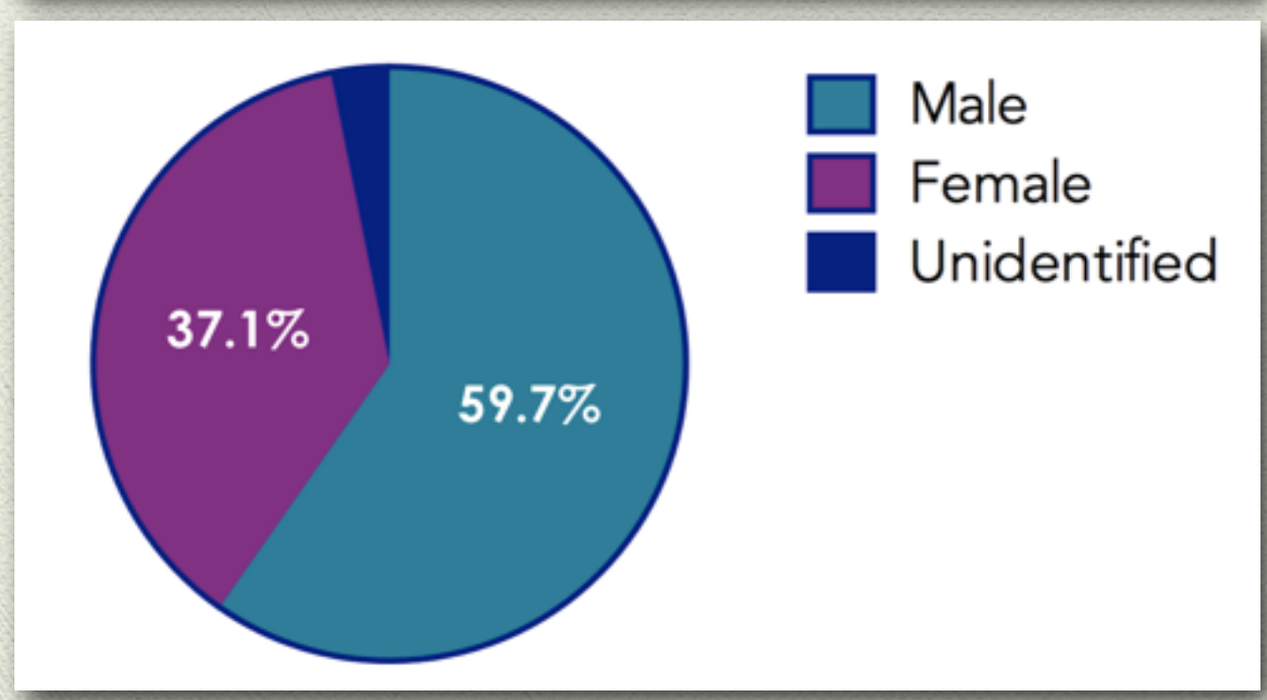
The Human Heart Physiology Program

(~400 human hearts)

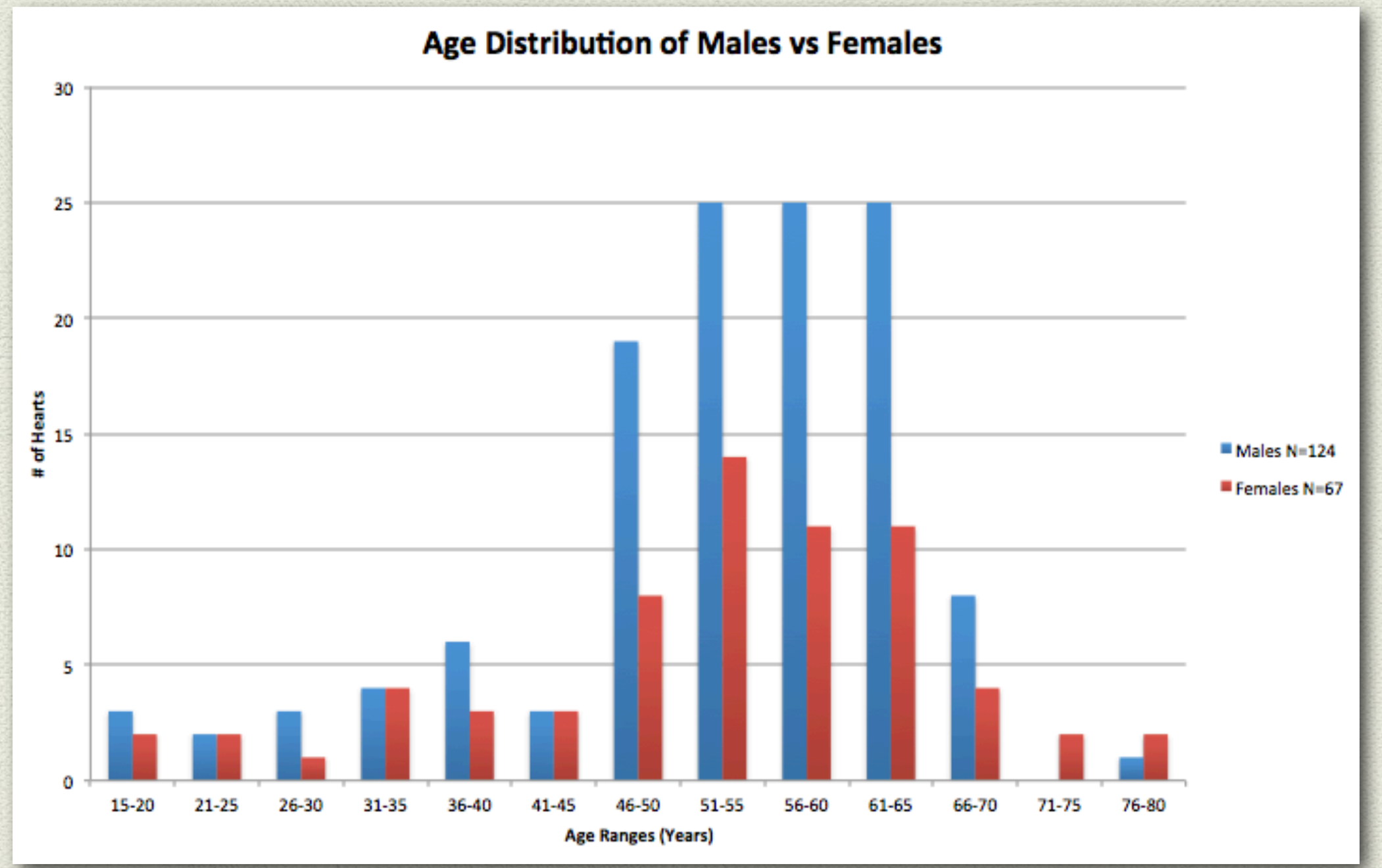




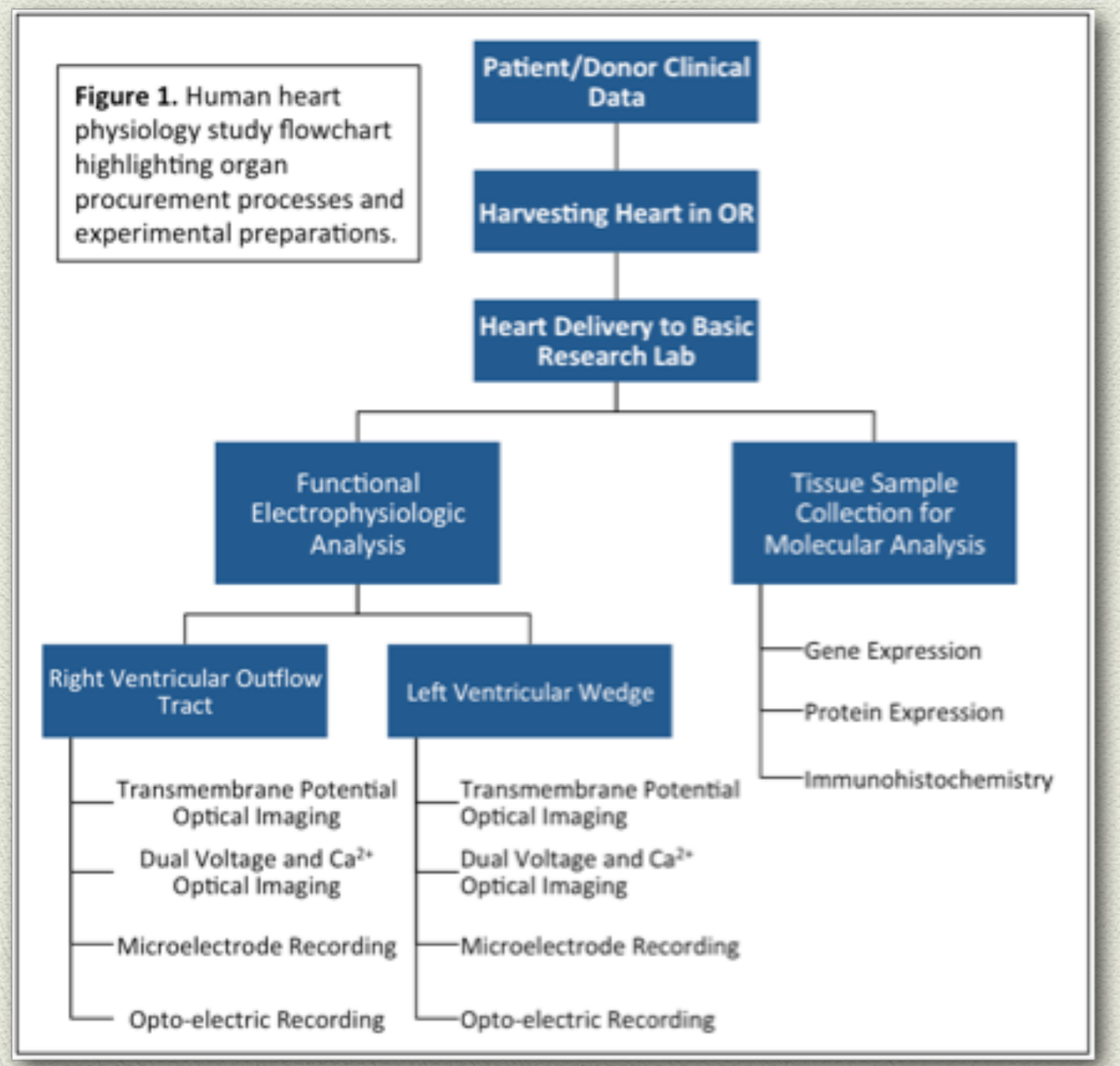




The Human Heart Physiology Program

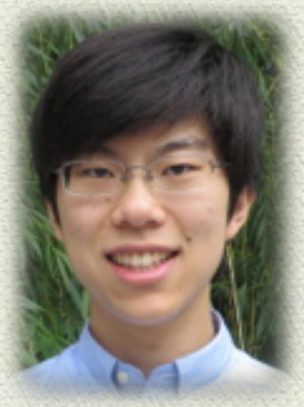


The Human Heart Physiology Program: Workflow Chart

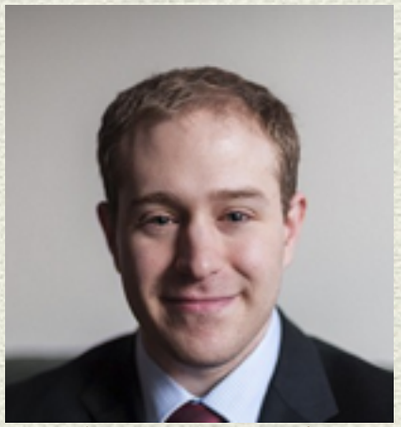


The Efimov Lab Human Heart Team


Jaclyn Brennan


Yun Qiao


Chaoyi Kang


Aaron Koppel


Kedar Aras

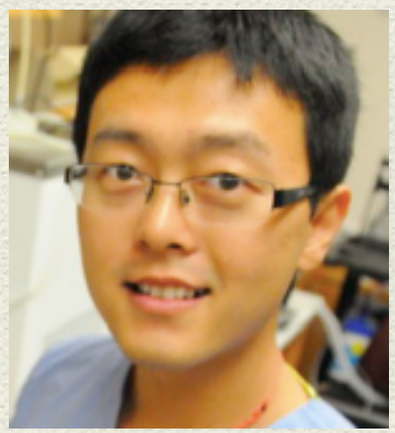

Chris Gloschat


Fu Siong Ng


Katherine Holzem

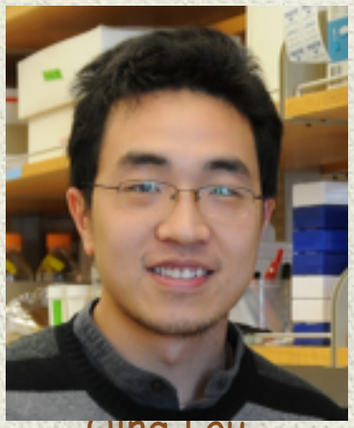

Megan Flake


Bas Boukens


Di Lang


Matt Sulkin


Christina Ambrosi


Qing Lou


Alexey Glukhov,


Vadim Fedorov


Bill Hucker


Debbie Janks

Published Projects:

1. Hucker WJ, McCain ML, Laughner JI, Iaizzo PA, Efimov IR, Connexin 43 Expression Delineates Two Discrete Pathways in the Human Atrioventricular Junction, Anat. Rec., 2008, 291(2): 204-15.
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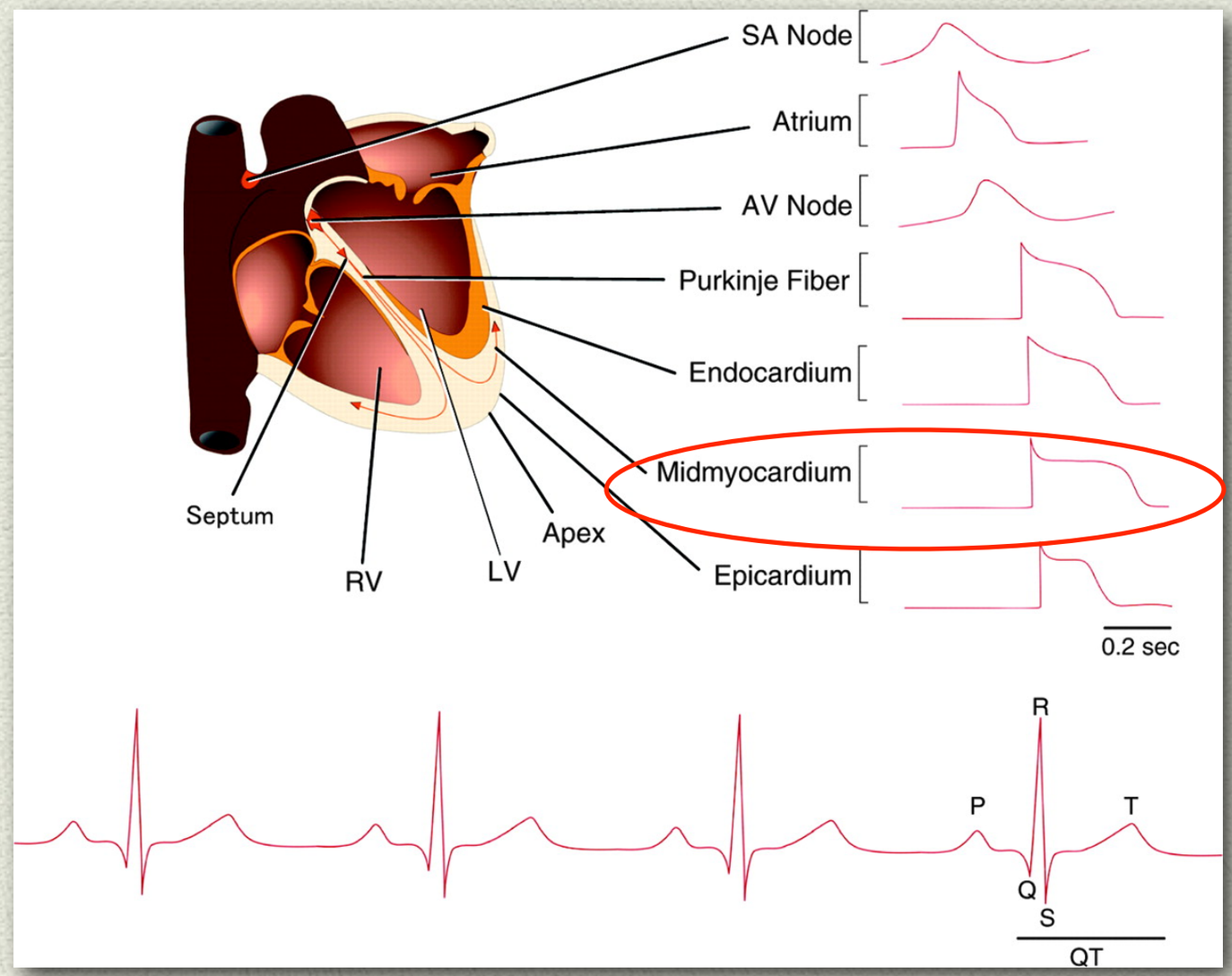
17. ...

Outline

- Need for studying human physiology
- Electrophysiology remodeling
- Metabolic remodeling
- Adrenergic remodeling
- New methodology

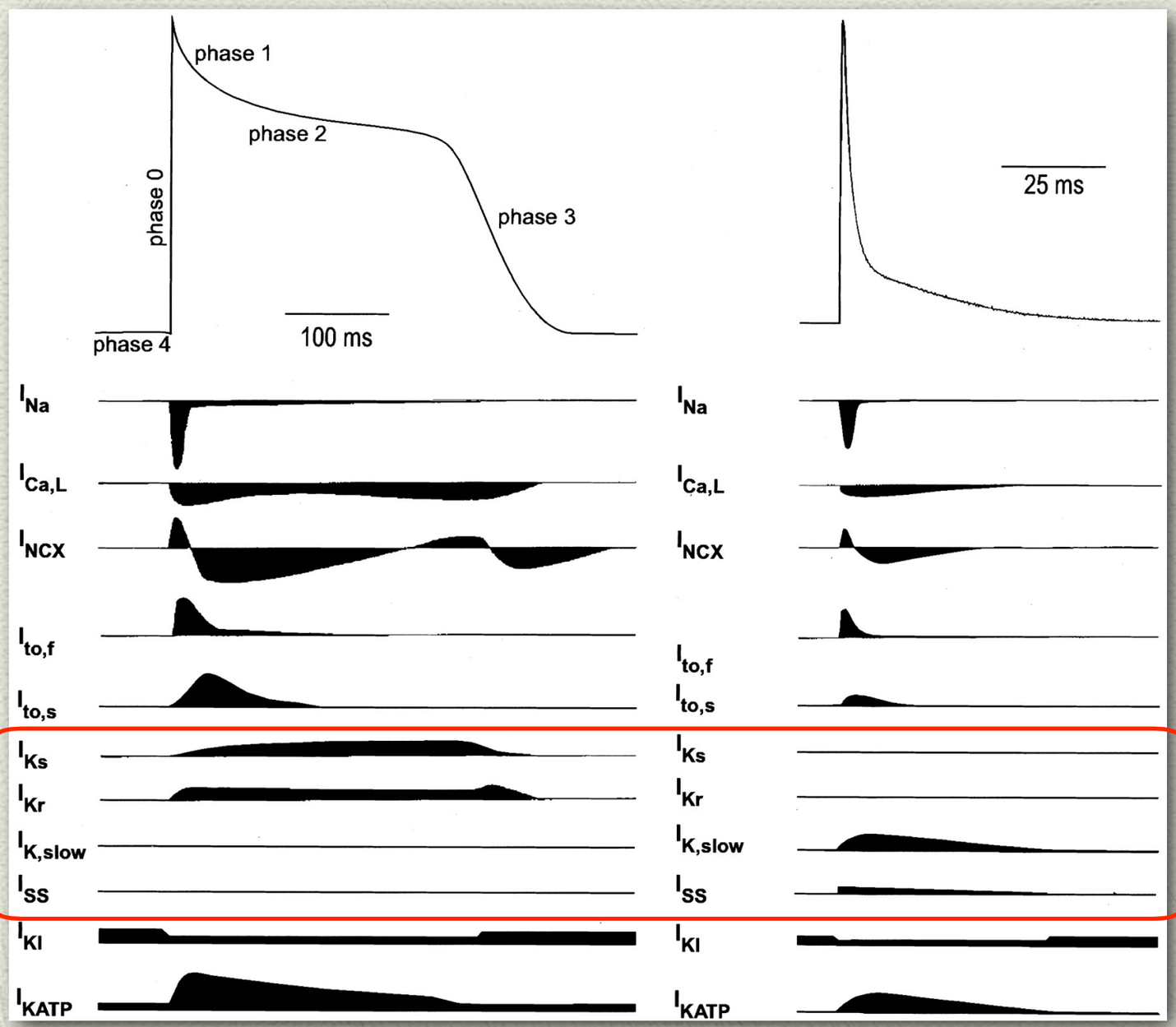
Human Heart Electrophysiology



Do M-cells exist?

Jeanne M. Nerbonne, and Robert S. Kass Physiol Rev 2005;85:1205-1253

Action Potentials and Underlying Ionic Currents in Human and Mouse Ventricular Myocytes

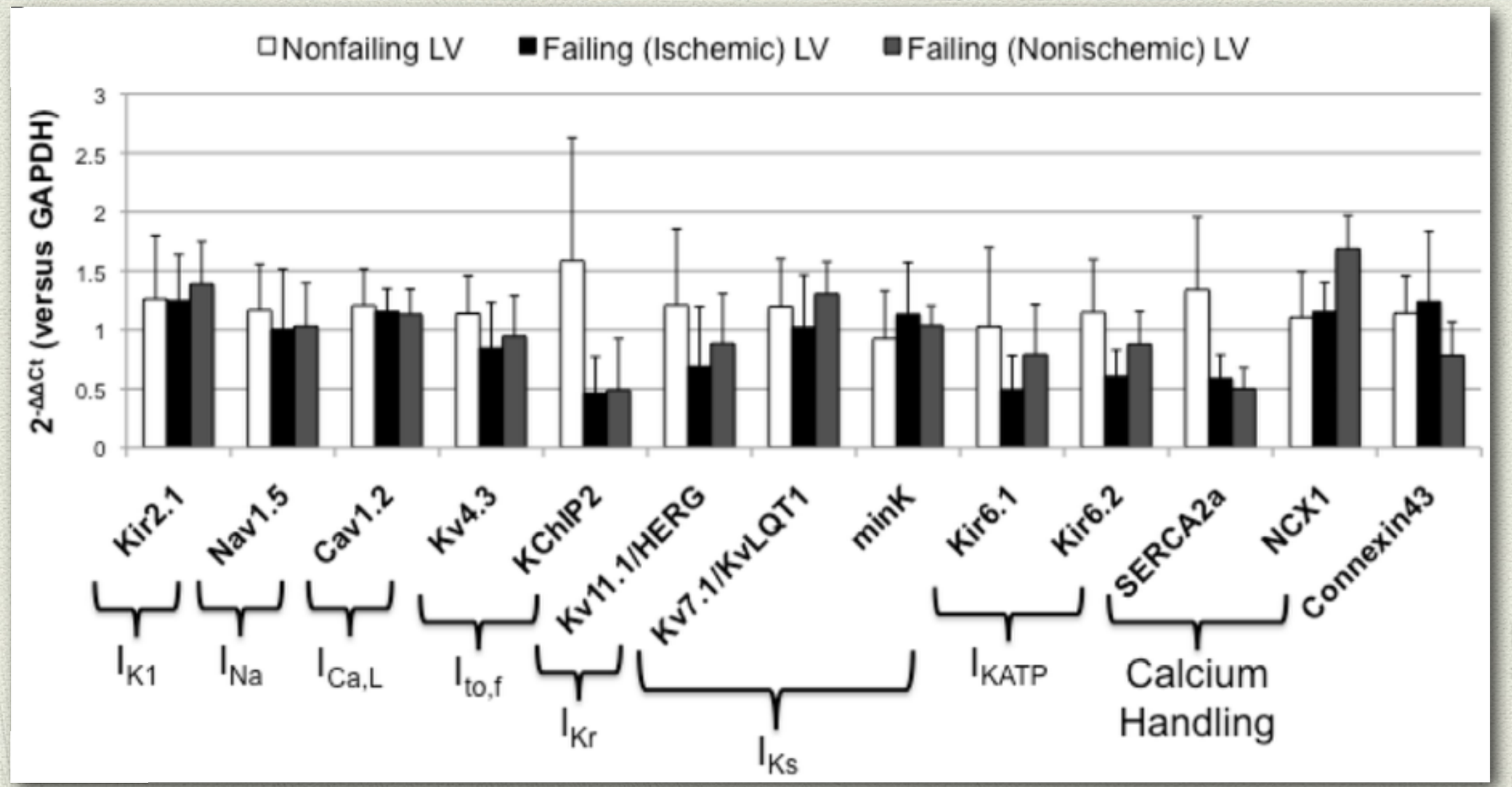


Jeanne M. Nerbonne et al. Circ Res. 2001;89:944-956

Human vs. Mouse: 60 versus 600 beats per minute

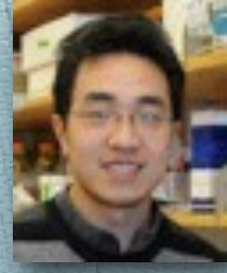
Human vs. Mouse: Potassium currents

Ventricular Remodeling of Major Ion Channel Subunits in Heart Failure

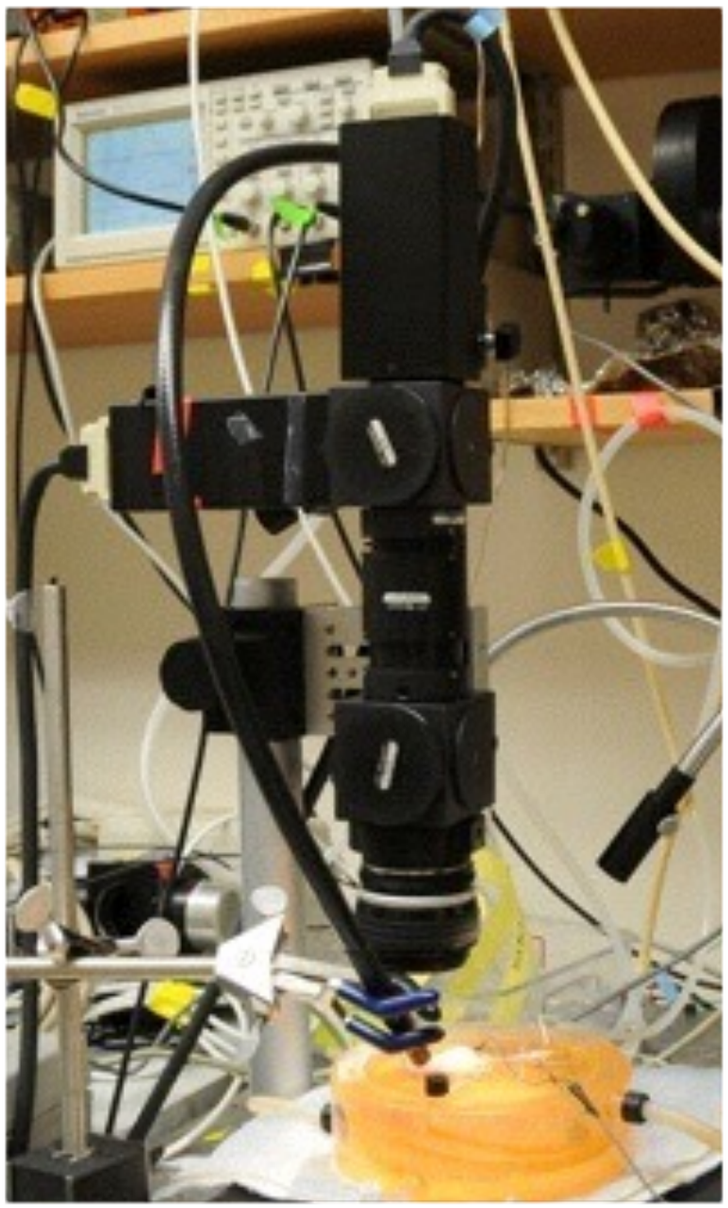


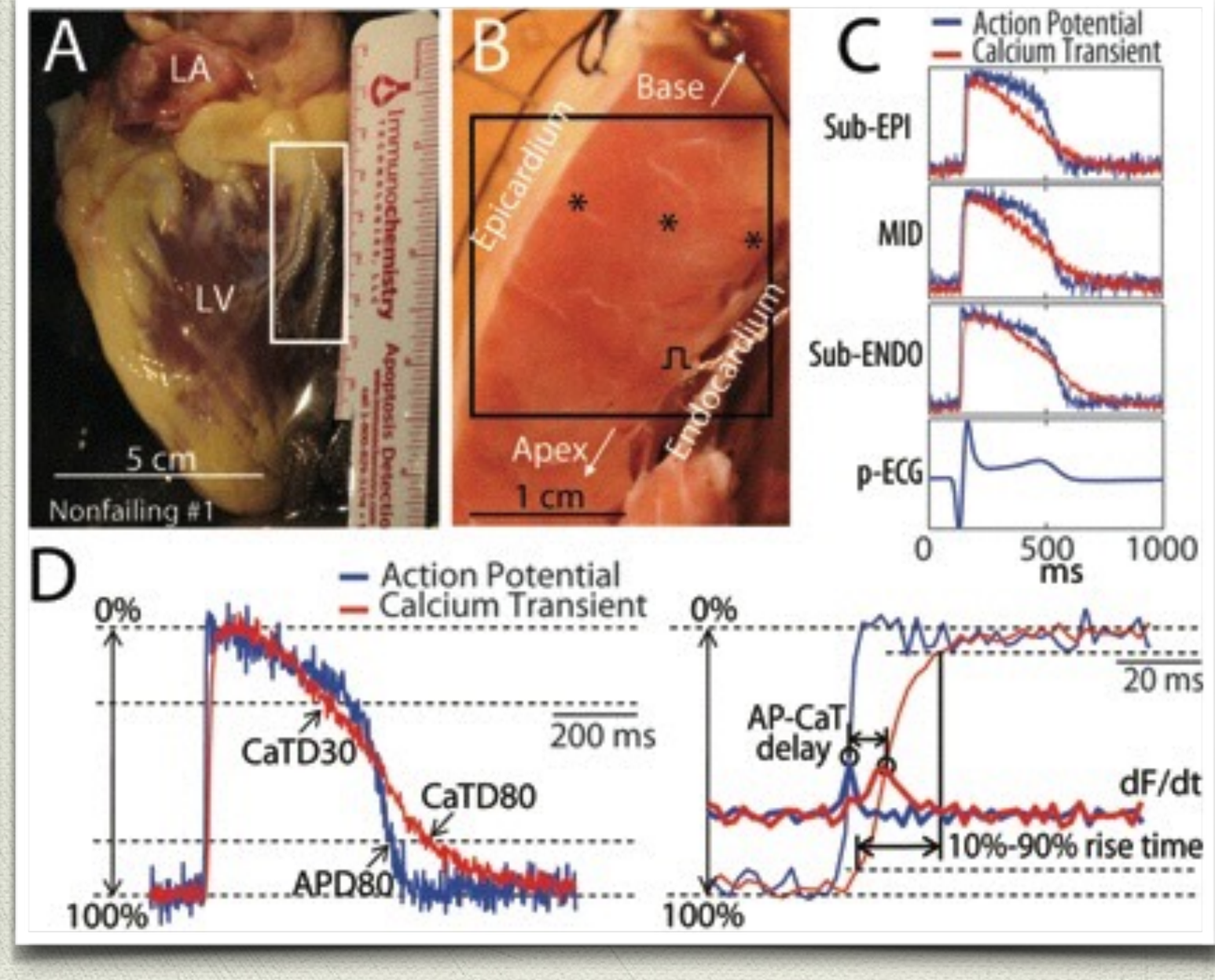
Ambrosi et al, Gender Dependent Differences in Molecular Electrophysiological Targets in Failing and Nonfailing Human Hearts, PLOS ONE; 2013

Simultaneous Mapping of Action Potentials and Calcium Transients in the Human Heart

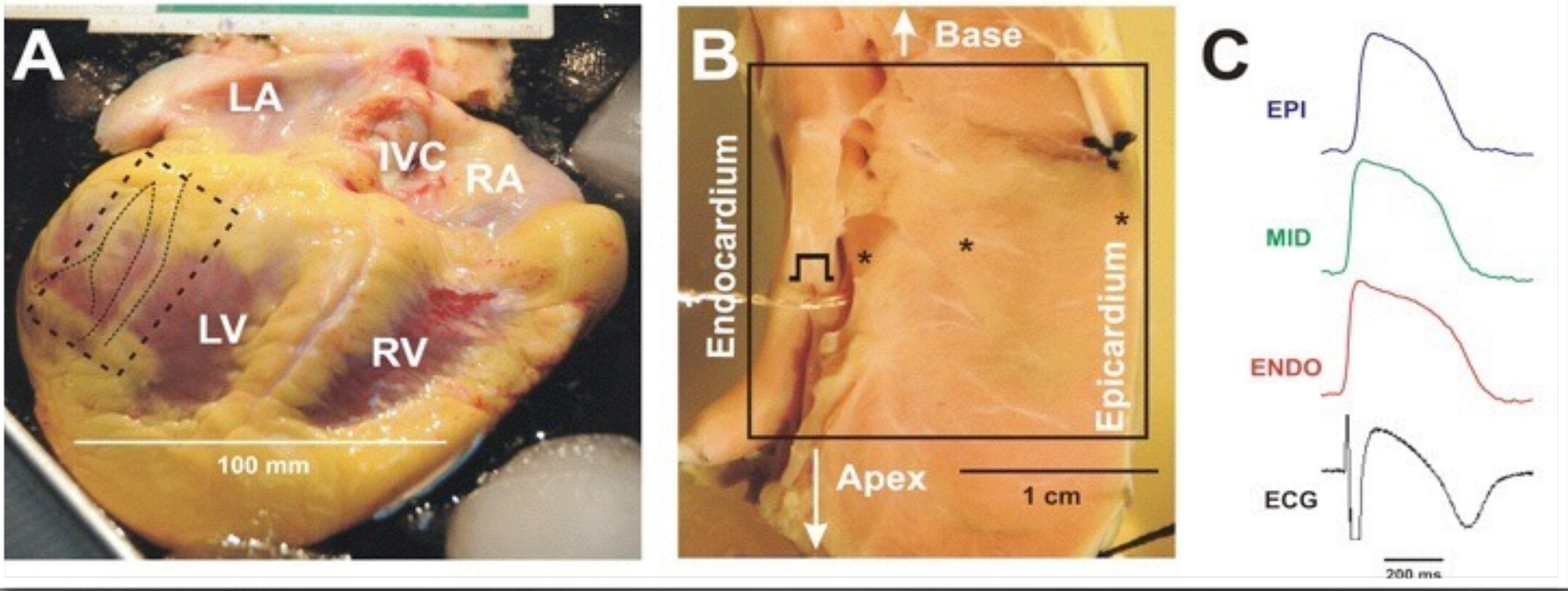


Lou,
Circulation, 2011





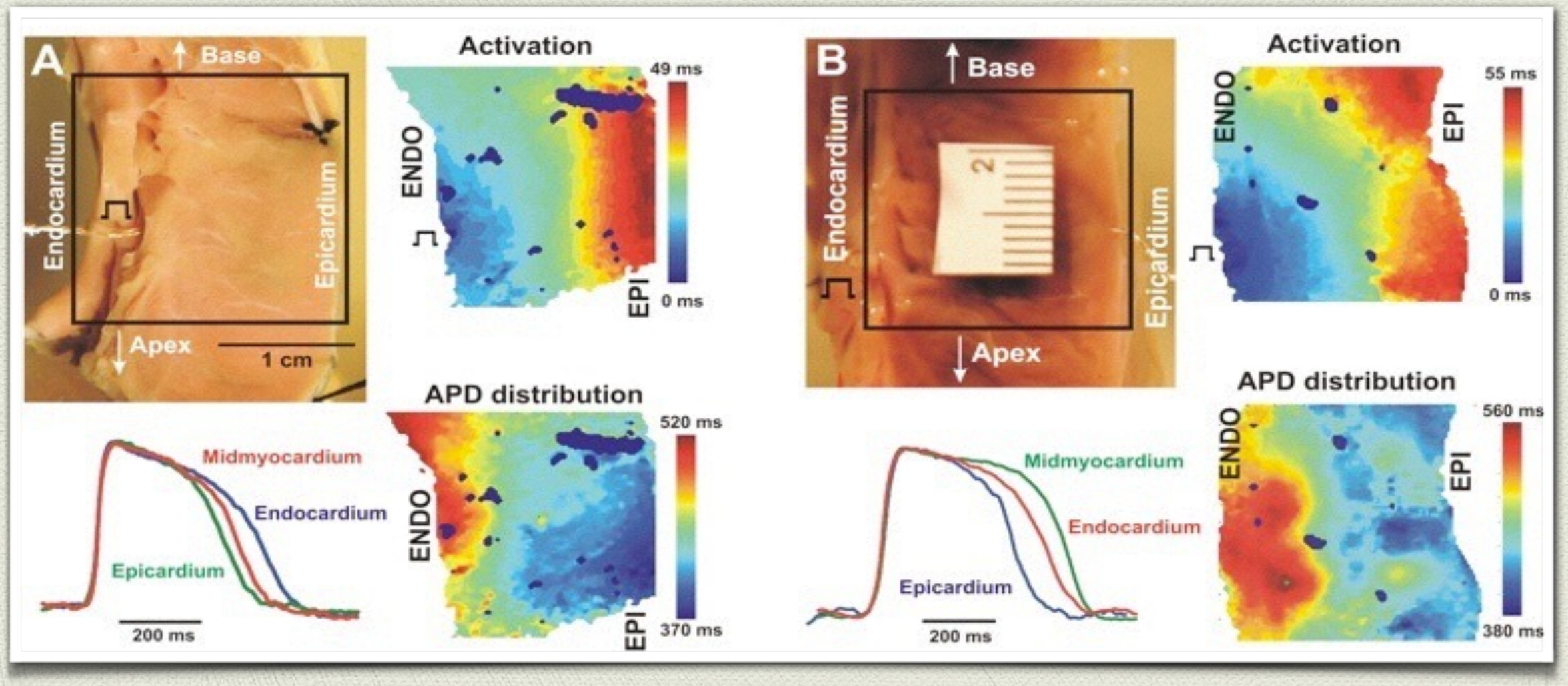
Electrophysiology of Failing and Donor Human Hearts



Glukhov, Circ. Res. 2010

No Evidence of M-cells in Human Hearts, but significant endo-to-epicardial APD gradient

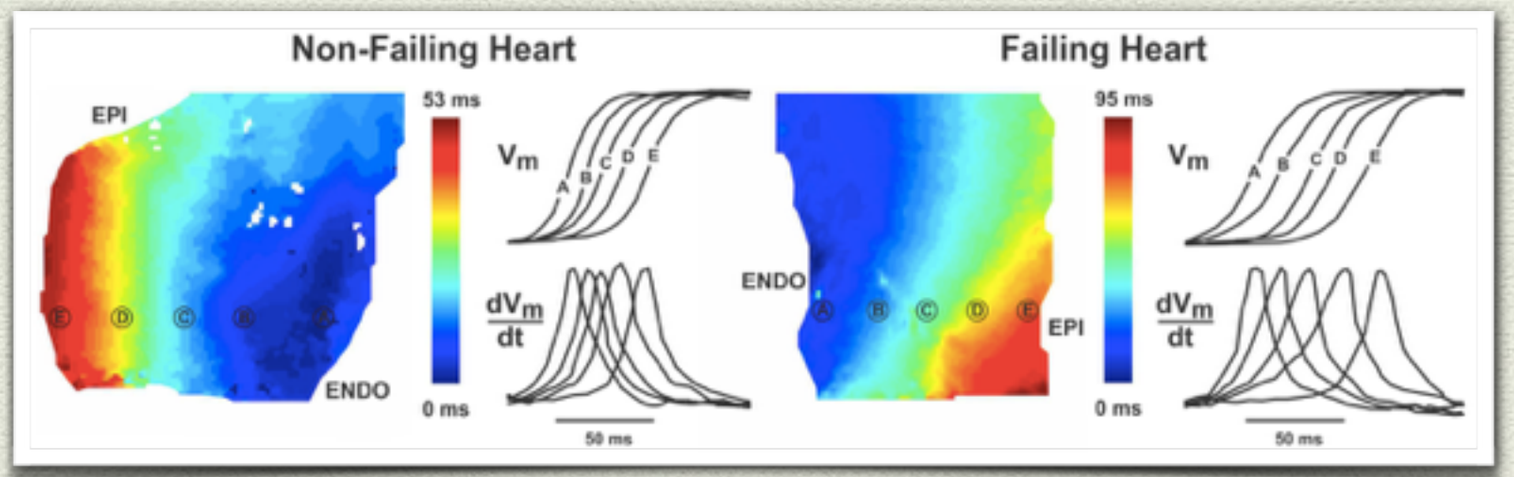
Glukhov,
Circ. Res. 2010

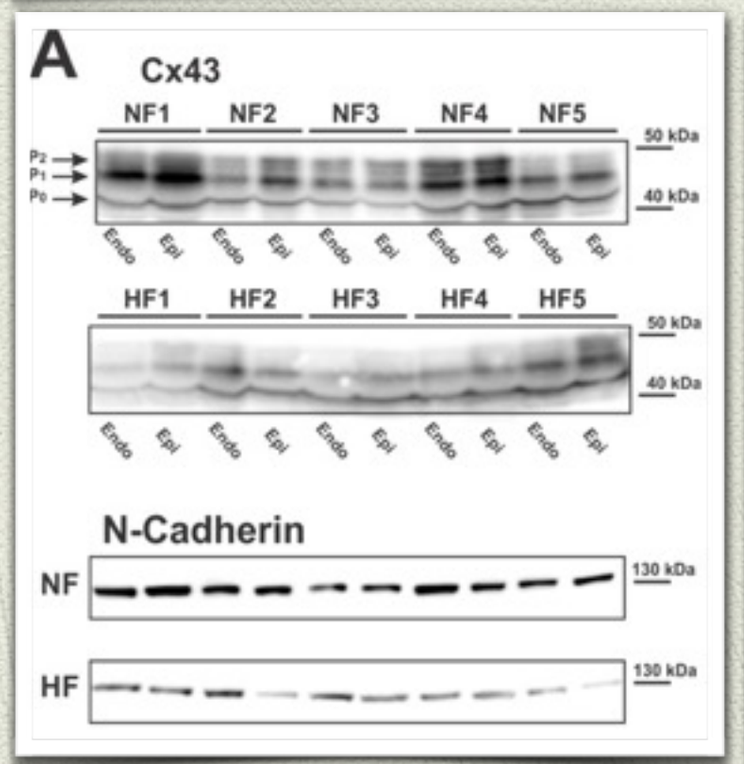


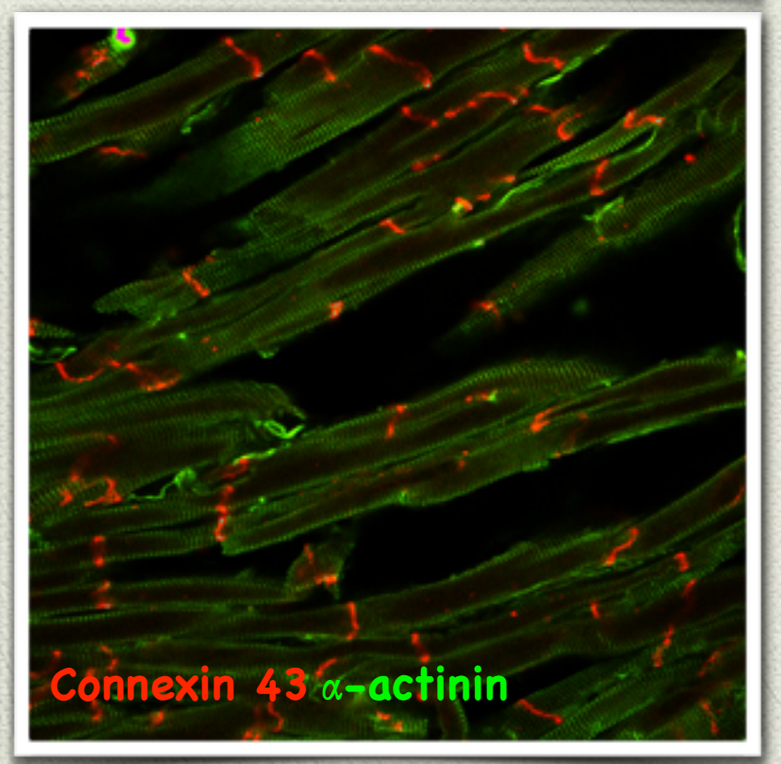
Female, age 33 Male, age 20

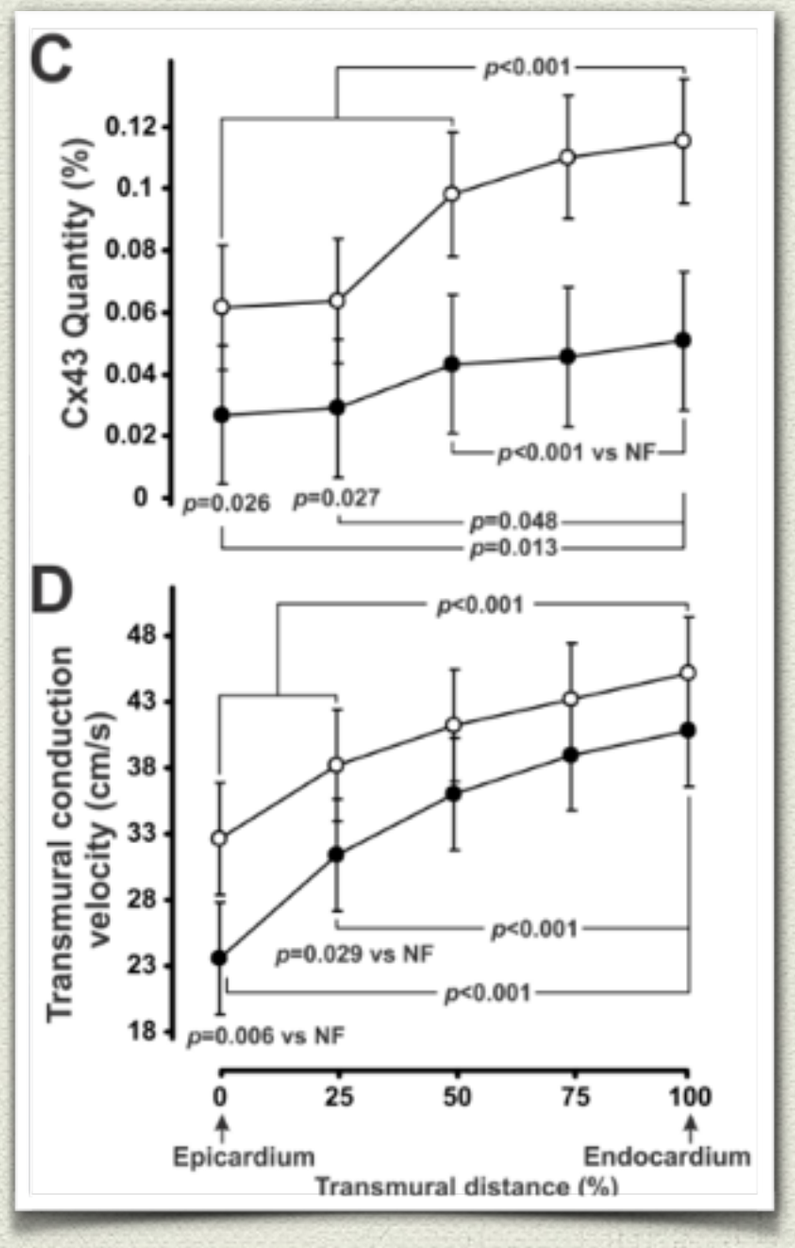
Transmural conduction slowing in failing heart is caused by Cx43 downregulation

Glukhov,
2012, Circulation



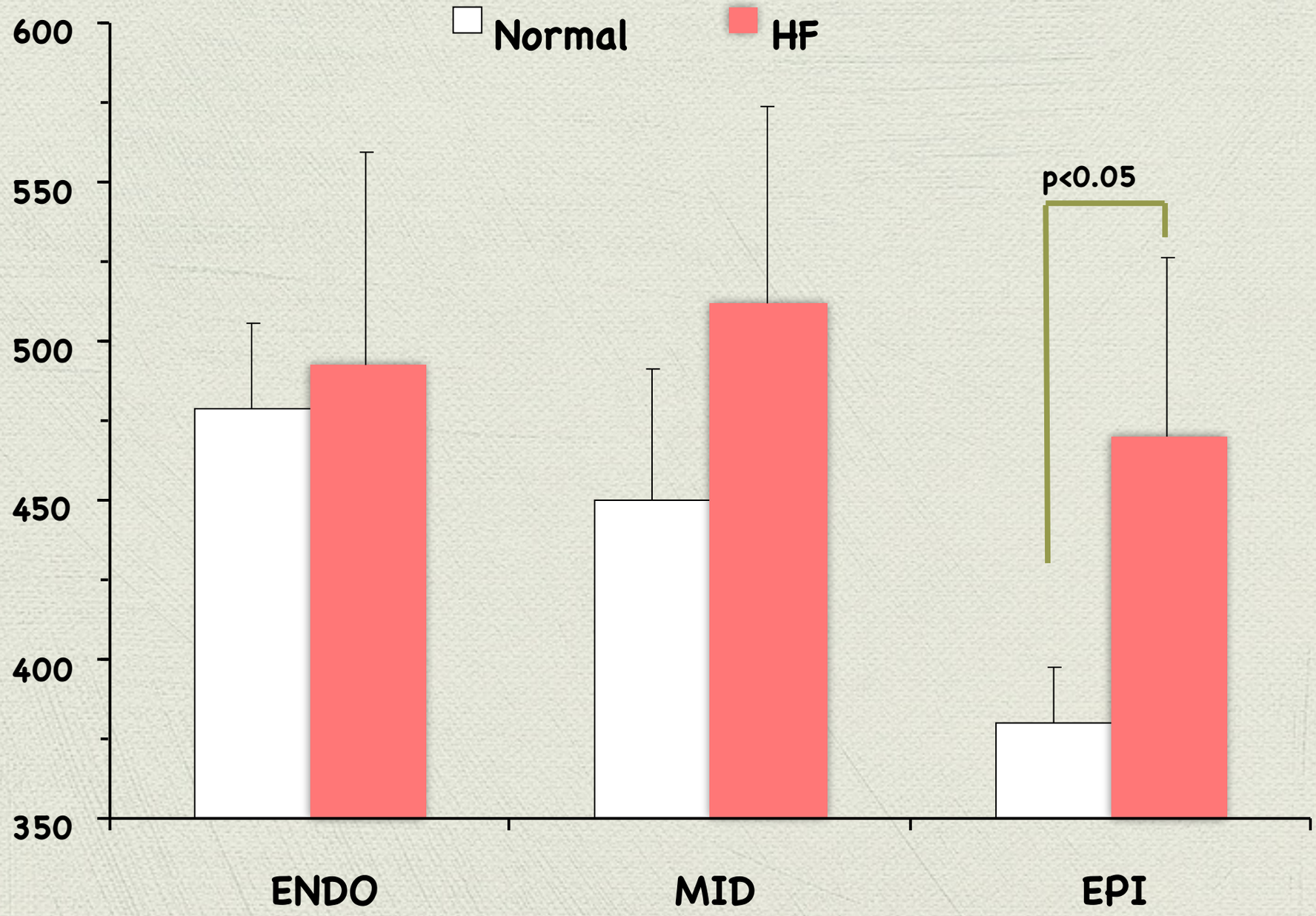


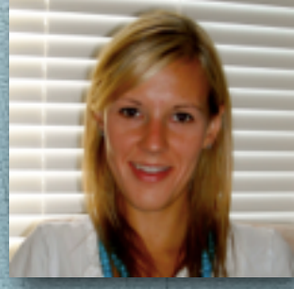




HF remodeling of APD: endocardium, mid-myocardium and epicardium

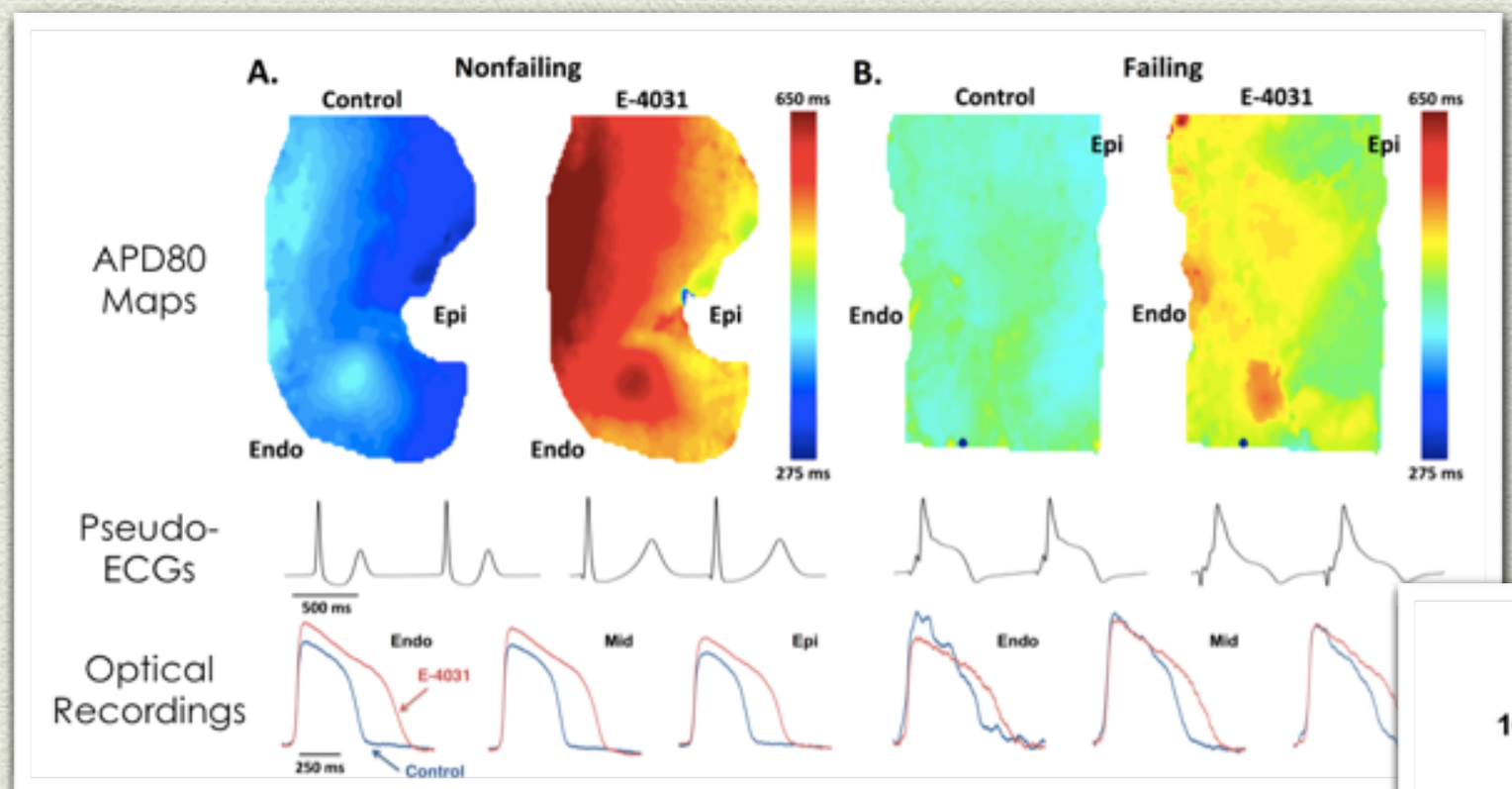
Glukhov,
Circ. Res. 2010

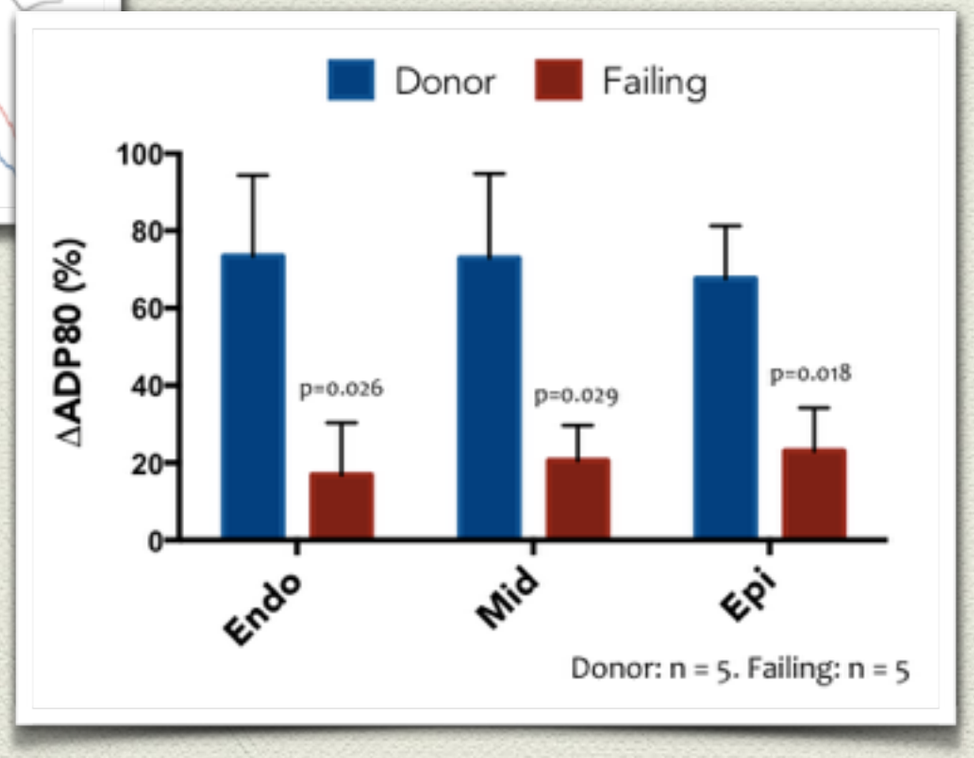




Holzem, JMCC 2015

Reduced ΔAPD with IKr blockade in HF



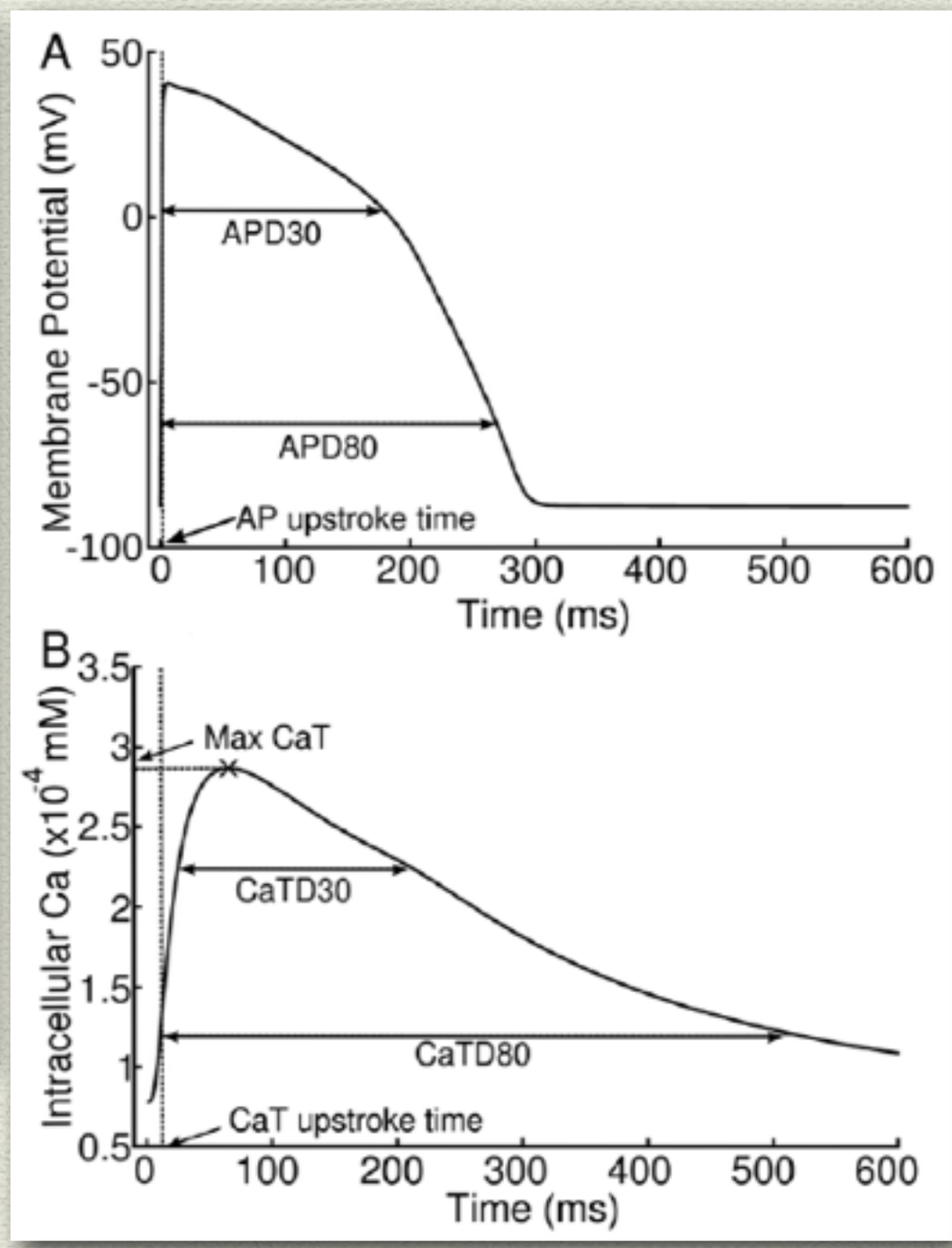


Human mRNA expression levels predict EP phenotype in heart failure

Table 1. Parameters under investigation.

Gene	Current	Parameter	Regulation in HF [3]
KChIP2	I_{to}, I_{CaL} (a)	G_{to}, G_{CaL}	↓
NCX1	I_{NaCa}	G_{NaCa}	↑ (b)
Serca2A	SERCA	J_{up}	↓
Kv4.3	I_{to}	G_{to}	↓ (c)
Kv11.1/HERG	I_{Kr}	G_{Kr}	↓ (c)
Kv7.1	I_{Ks}	G_{Ks}	–
Kir2.1	I_{K1}	G_{K1}	–

a) *KChIP2* has recently been shown to form an accessory subunit of I_{CaL} [40].
b) *NCX1* was downregulated in non-ischæmic cardiac myopathy patients but showed no difference from the non-failing group in ischæmic cardiac myopathy.
c) *Kv4.3* and *HERG* tended to be downregulated relative to the non-failing group however the difference was not statistically significant.
doi:10.1371/journal.pone.0056359.t001



Walmsley1 et al, mRNA Expression Levels in Failing Human Hearts Predict Cellular Electrophysiological Remodeling: A Population-Based Simulation Study. PLOS ONE, 2013

Action Potentials and Calcium Transients in human patient-specific model based on mRNA expression

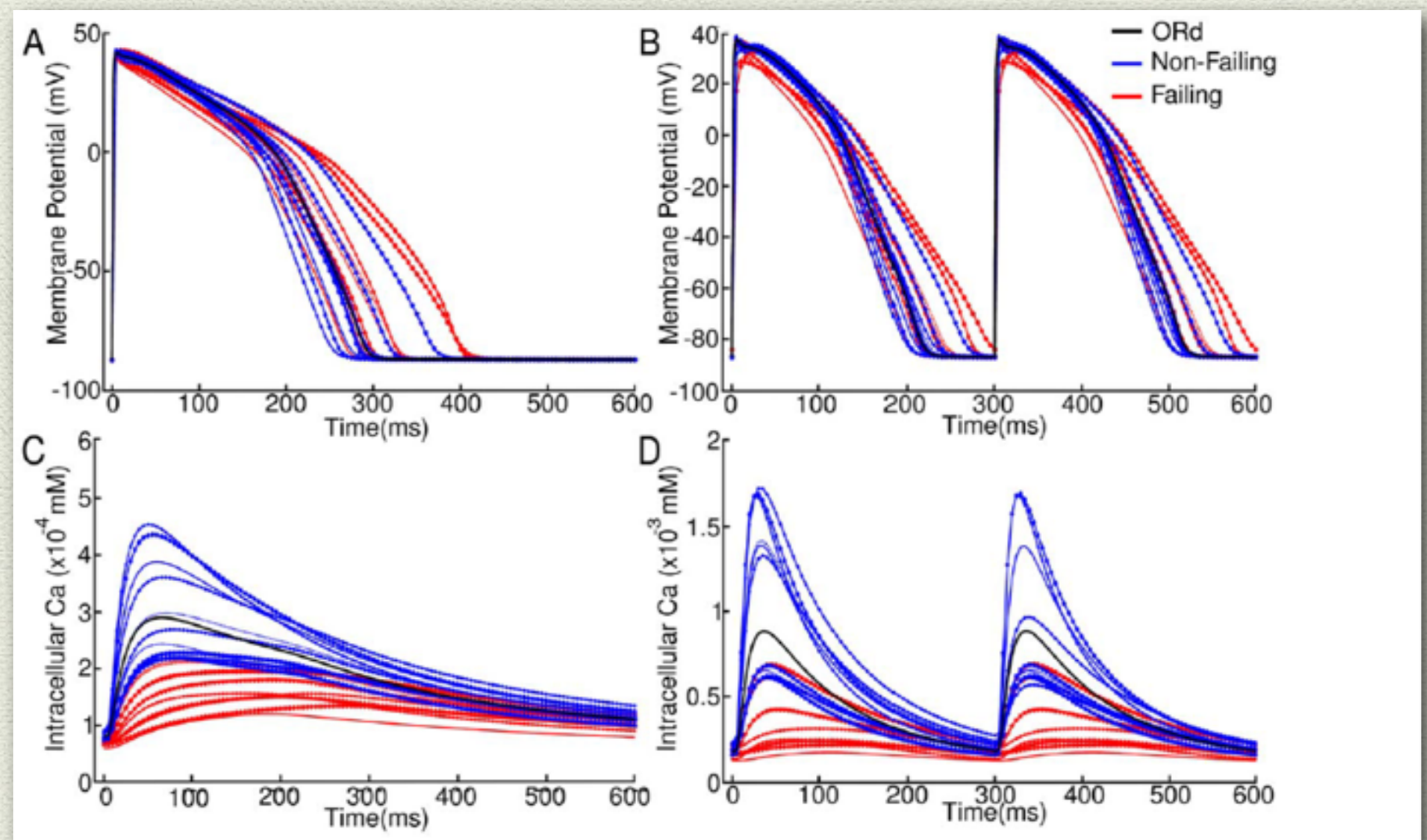
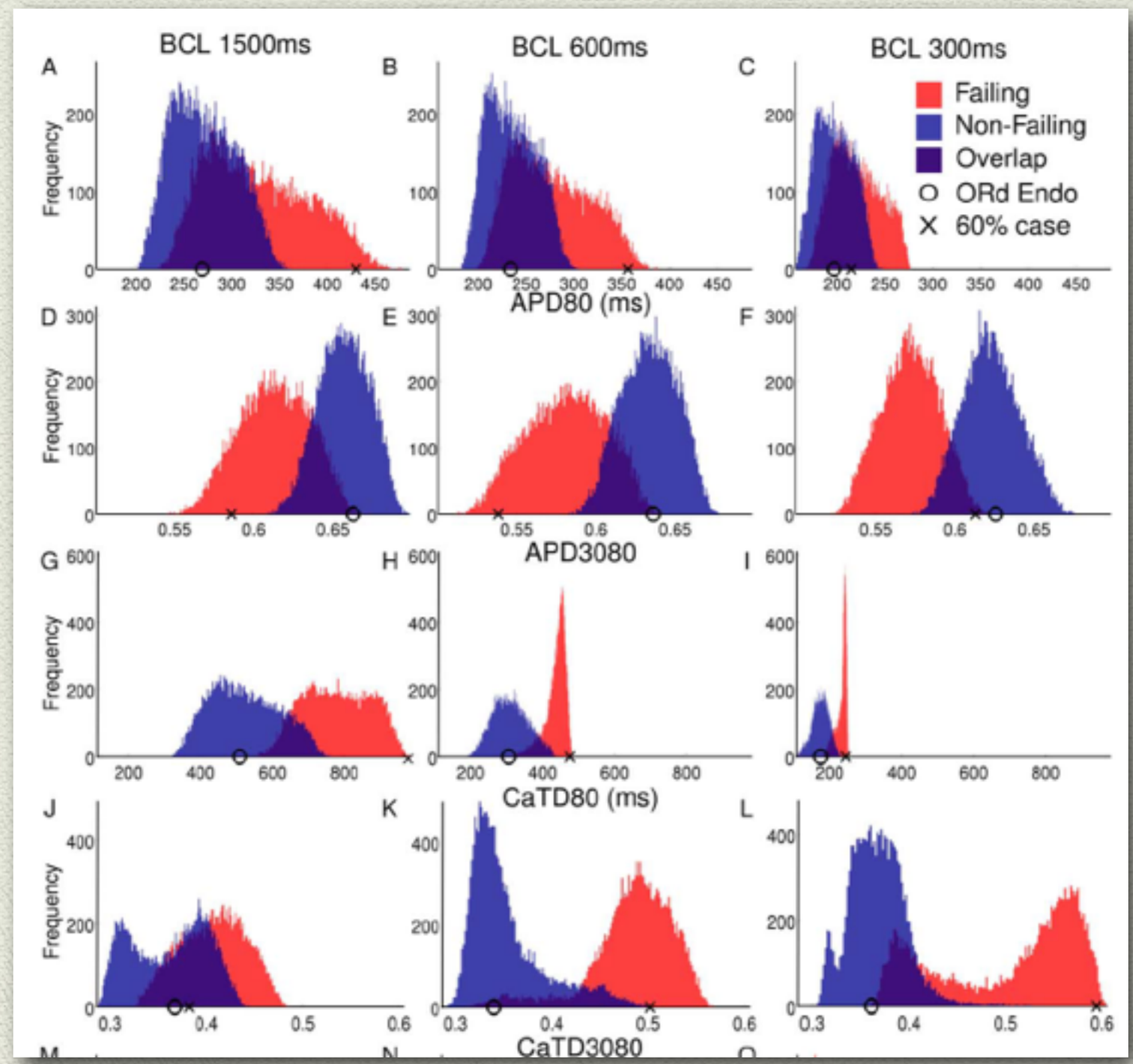


Figure 2. Sample AP and CaT traces obtained from the non-failing (blue) and failing (red) populations. Traces are shown for BCL = 1500 (A,C) and 300 ms (B,D). The AP for the standard ORd endocardial model is shown in black.
doi:10.1371/journal.pone.0056359.g002

Walmsley1 et al, mRNA Expression Levels in Failing Human Hearts Predict Cellular Electrophysiological Remodeling: A Population-Based Simulation Study. PLOS ONE, 2013

Histograms showing biomarker values obtained for the non-failing (blue) and failing (red) cell model populations



Walmsley1 et al, mRNA Expression Levels in Failing Human Hearts Predict Cellular Electrophysiological Remodeling: A Population-Based Simulation Study. PLOS ONE, 2013

Correlation plots of one biomarker against another

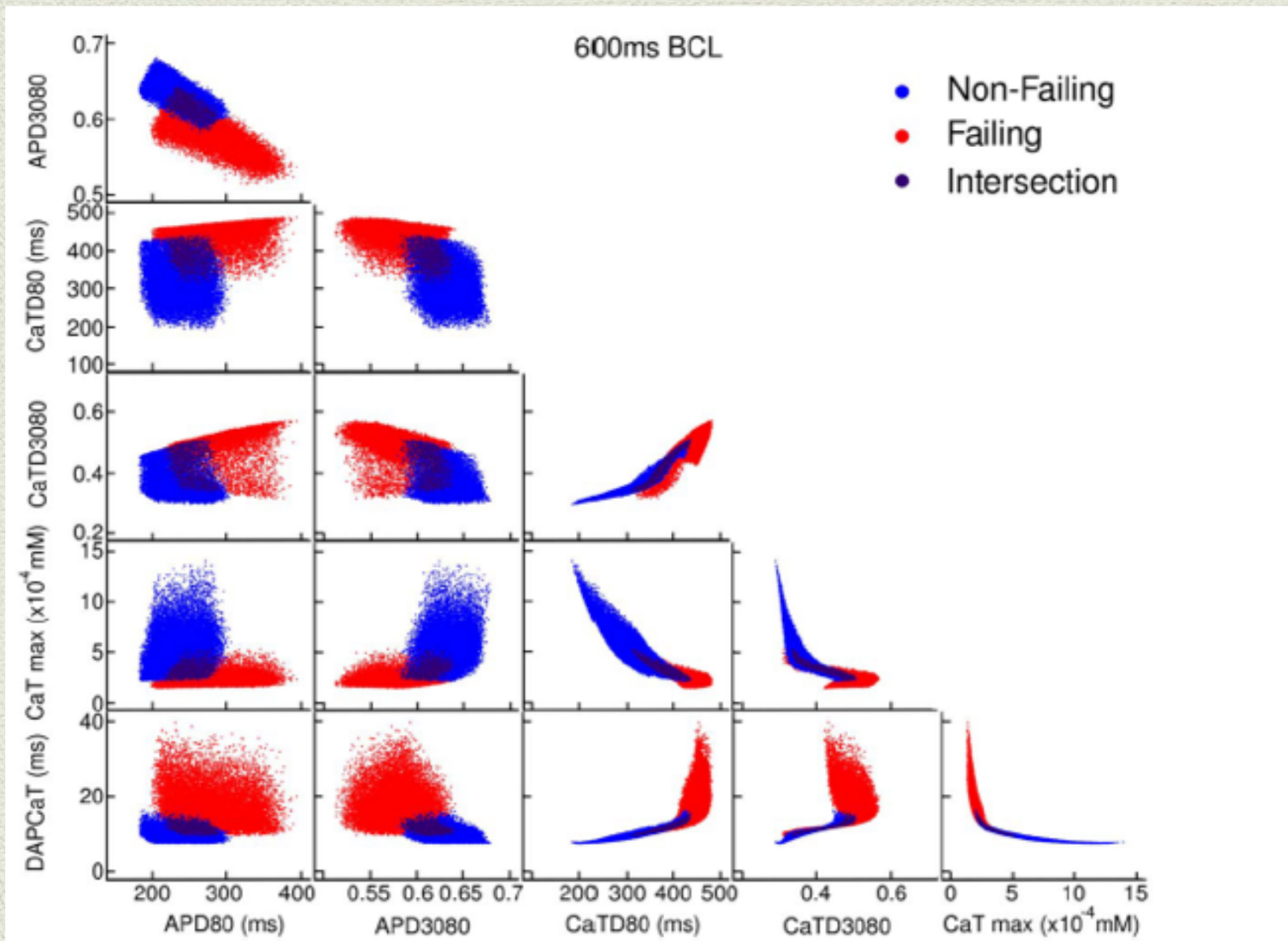


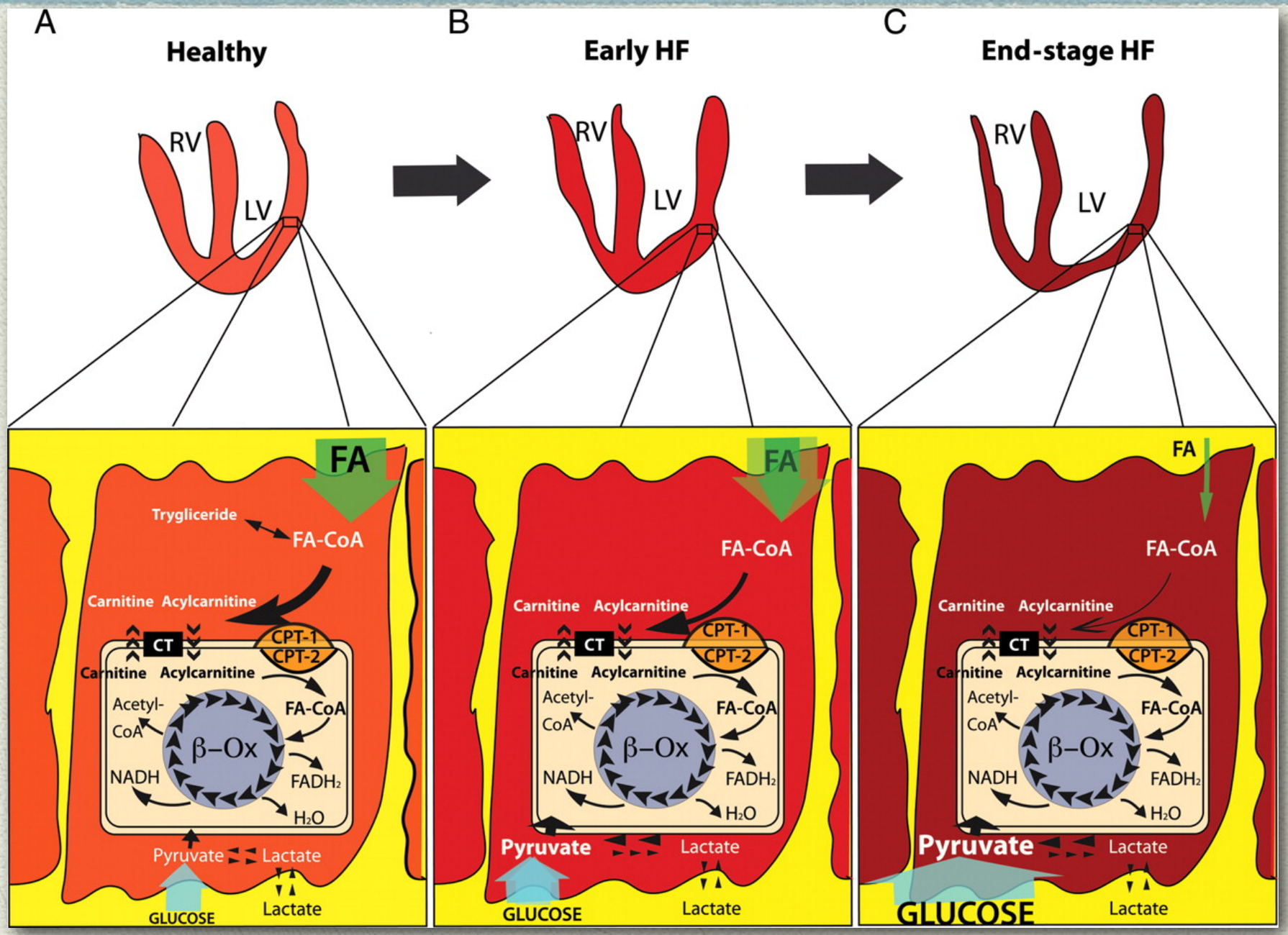
Figure 4. Correlation plots of one biomarker against another at 600 ms BCL. Red denotes the failing population, blue denotes the non-failing population, and the darker shade represents cells lying in the intersection between the two populations. Points which develop alternans are removed from these plots. Each biomarker is plotted against each other.
doi:10.1371/journal.pone.0056359.g004

Walmsley1 et al, mRNA Expression Levels in Failing Human Hearts Predict Cellular Electrophysiological Remodeling: A Population-Based Simulation Study. PLOS ONE, 2013

Outline

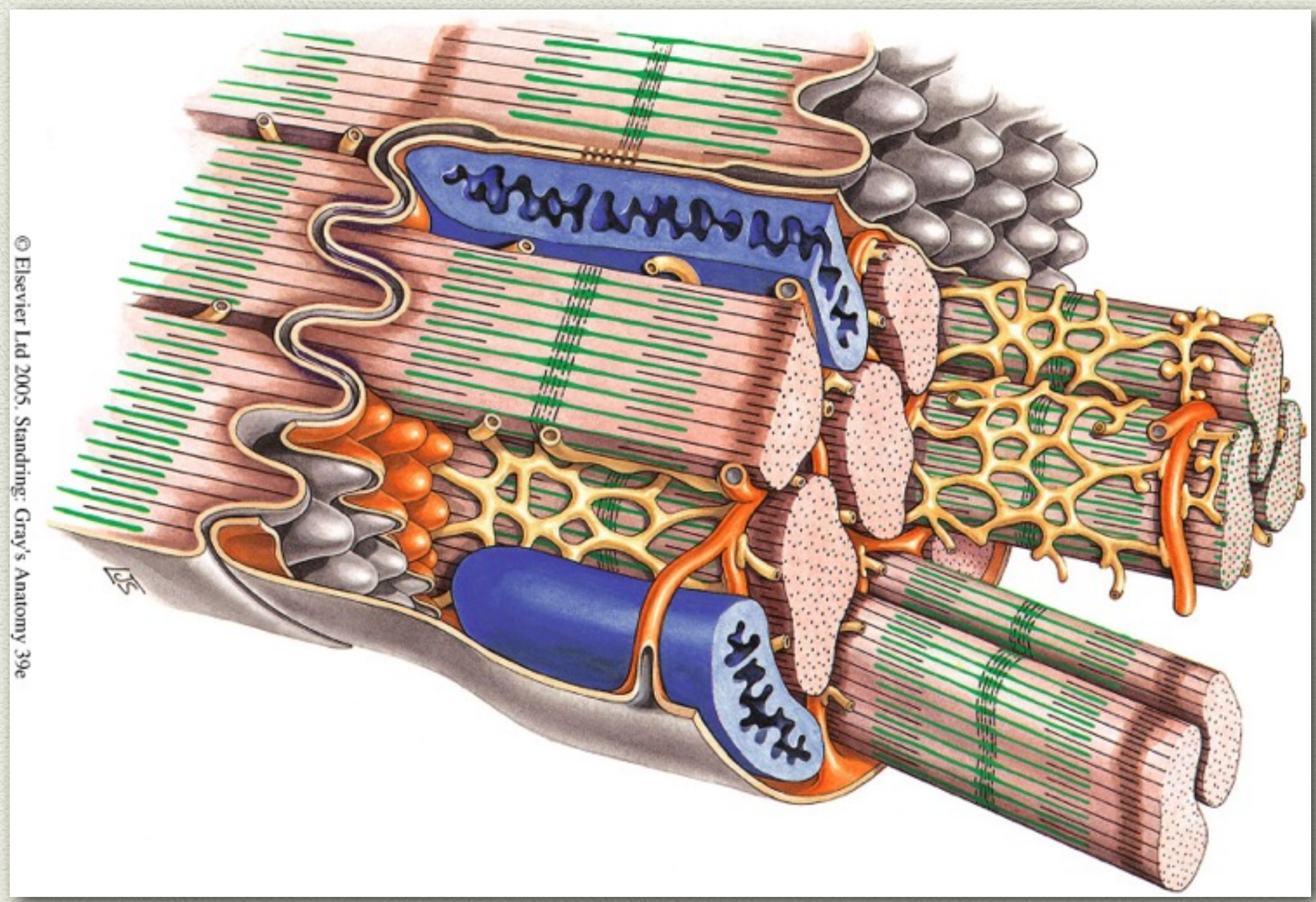
- Need for studying human physiology
- Electrophysiology remodeling
- Metabolic remodeling
- Adrenergic remodeling
- New methodology

Metabolic Shift of Substrate Utilization in Heart Failure from Fatty Acids to Carbs

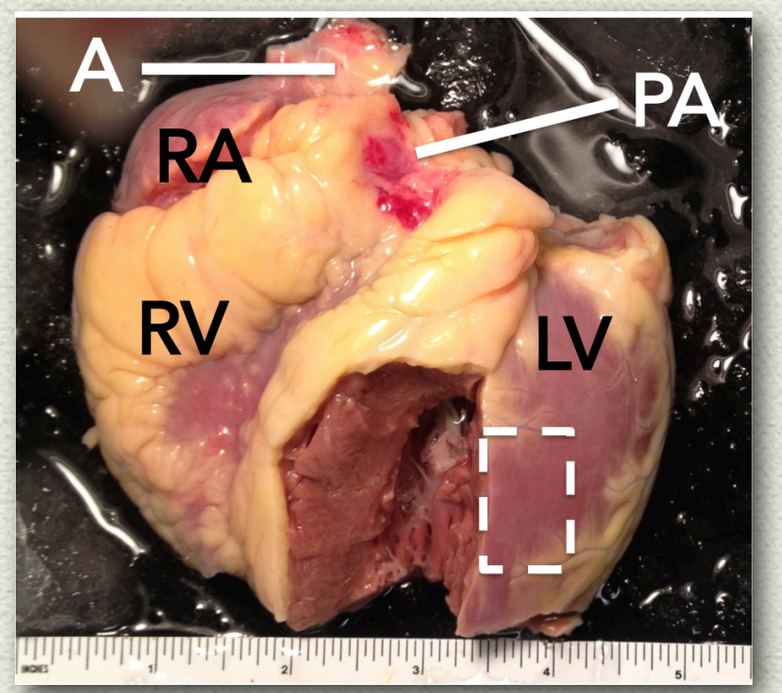


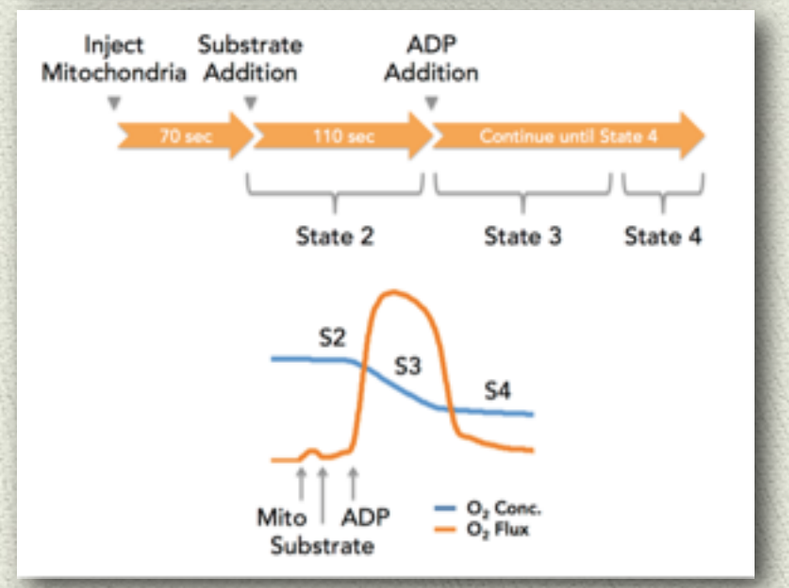
Lionetti et al, Cardiovasc. Res. 2011

Textbook structure of a muscle cell



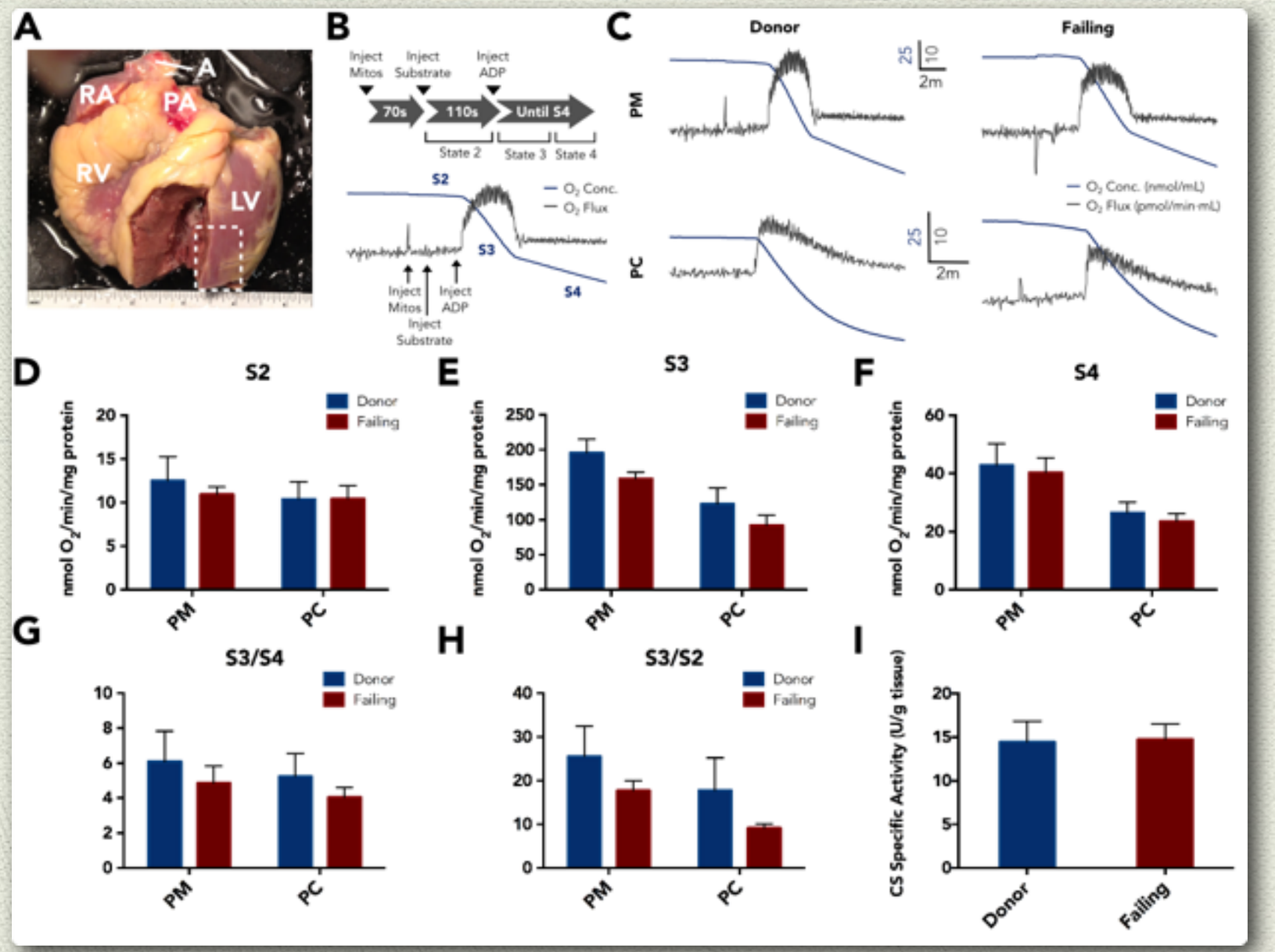
Human Mitochondrial Respiration Measurement Protocol





- Hearts were recovered in the OR and immediately arrested with ice-cold cardioplegia
- Anterior LV region (white box) was dissected and minced
- Mitochondria were isolated via differential centrifugation
- Respiration measurements were collected on an Oroboros Oxygraph with pyruvate/malate (PM) or palmitoylcarnitine (PC) as substrates
- Citrate synthase assay normalization
- Collaboration with Dan Beard and Kalyan Vinnakota, U Mich.

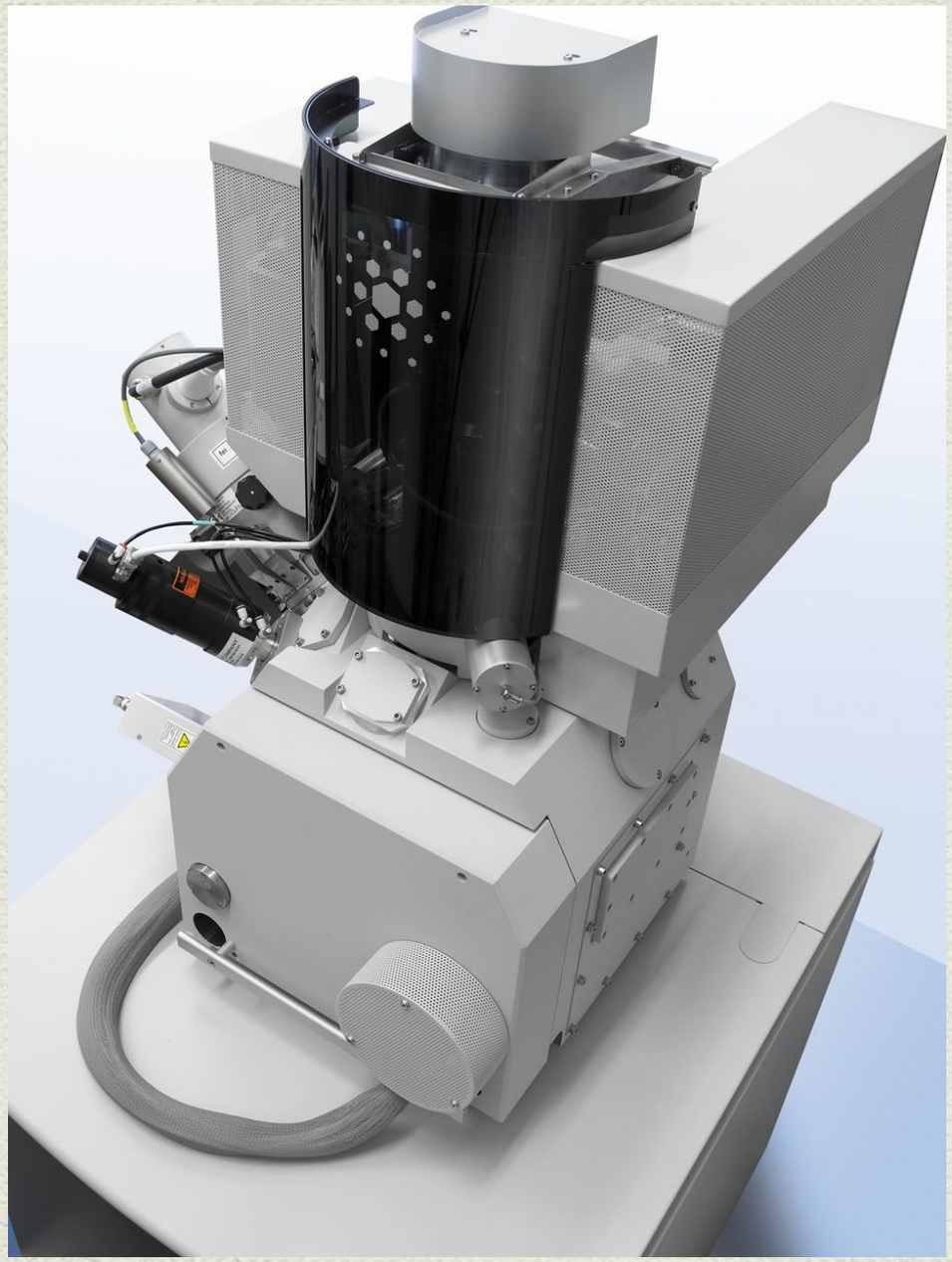
No evidence of decline in mitochondrial respiration in failing human LV



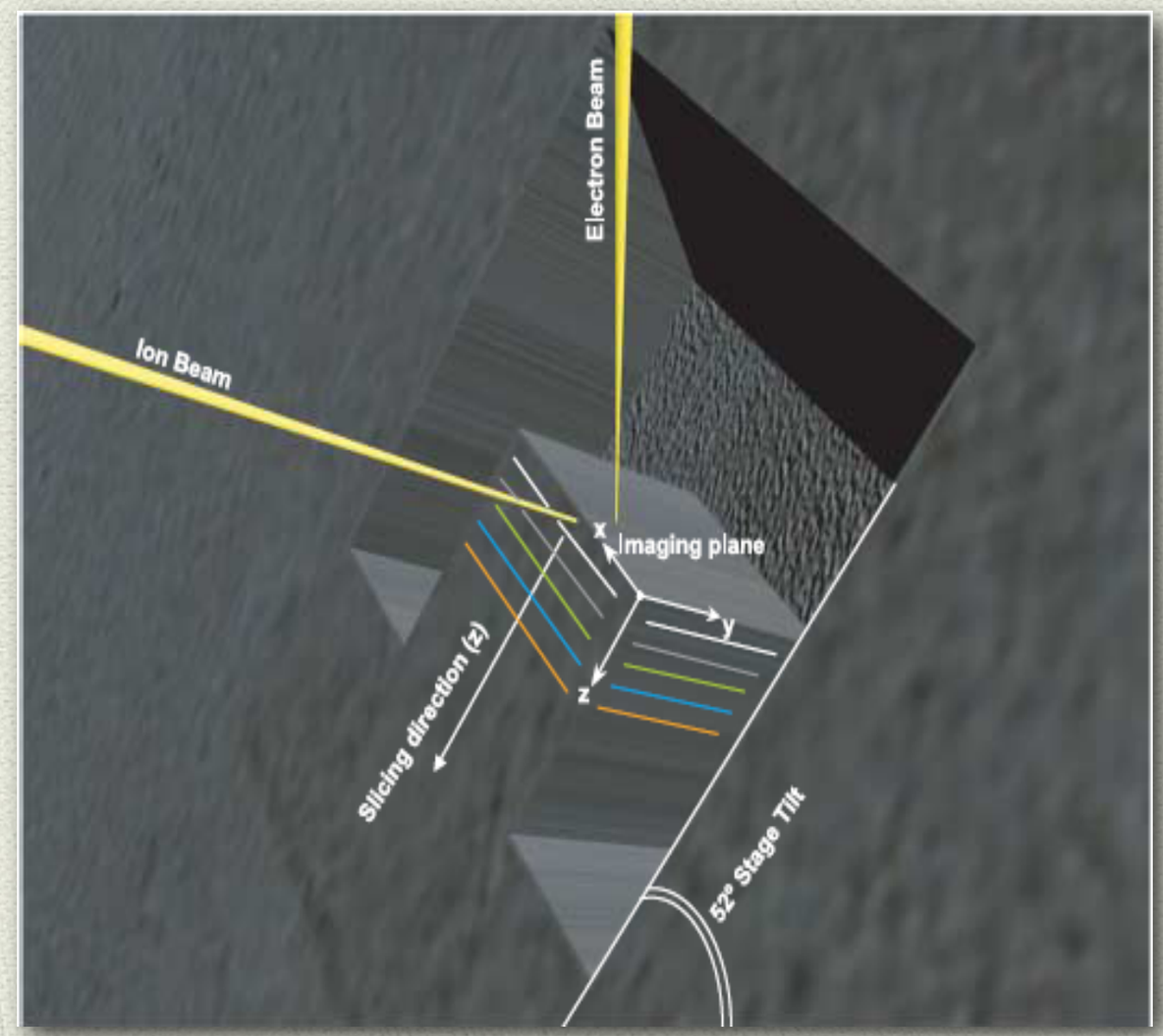
PM: pyruvate/malate; PC: palmitoylcarnitine.

FEI Helios NanoLab DualBeam™

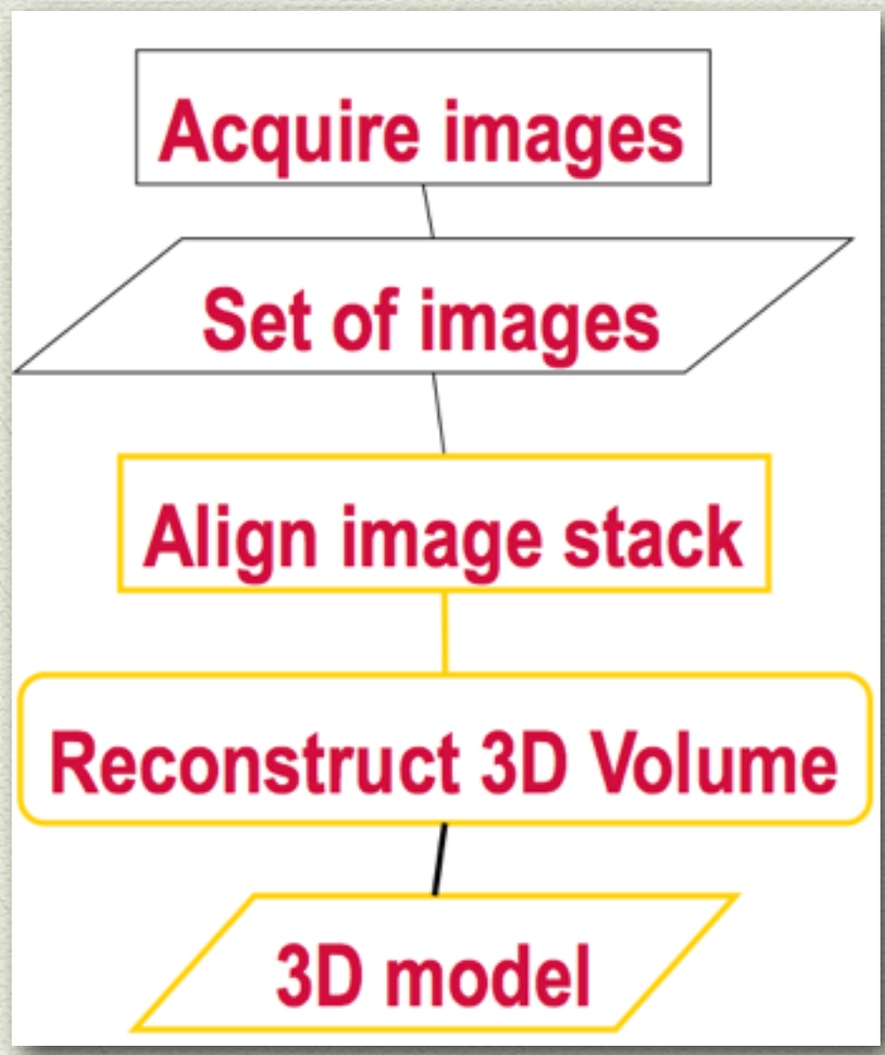
- SEM Resolution
  - 0.9 nm at 15 keV
  - 1.4 nm at 1 keV
- E beam energy: 350 eV – 30 keV
- E beam current: <= 22 nA
- I beam energy: 500 eV – 30 keV
- I beam current: 1.5 pA – 20 nA
  - (optional up to 65 nA available)
- FIB Resolution
  - 5 nm at 30 keV
- 5 axis, 6” piezo stage in x,y (+/- 1μm)



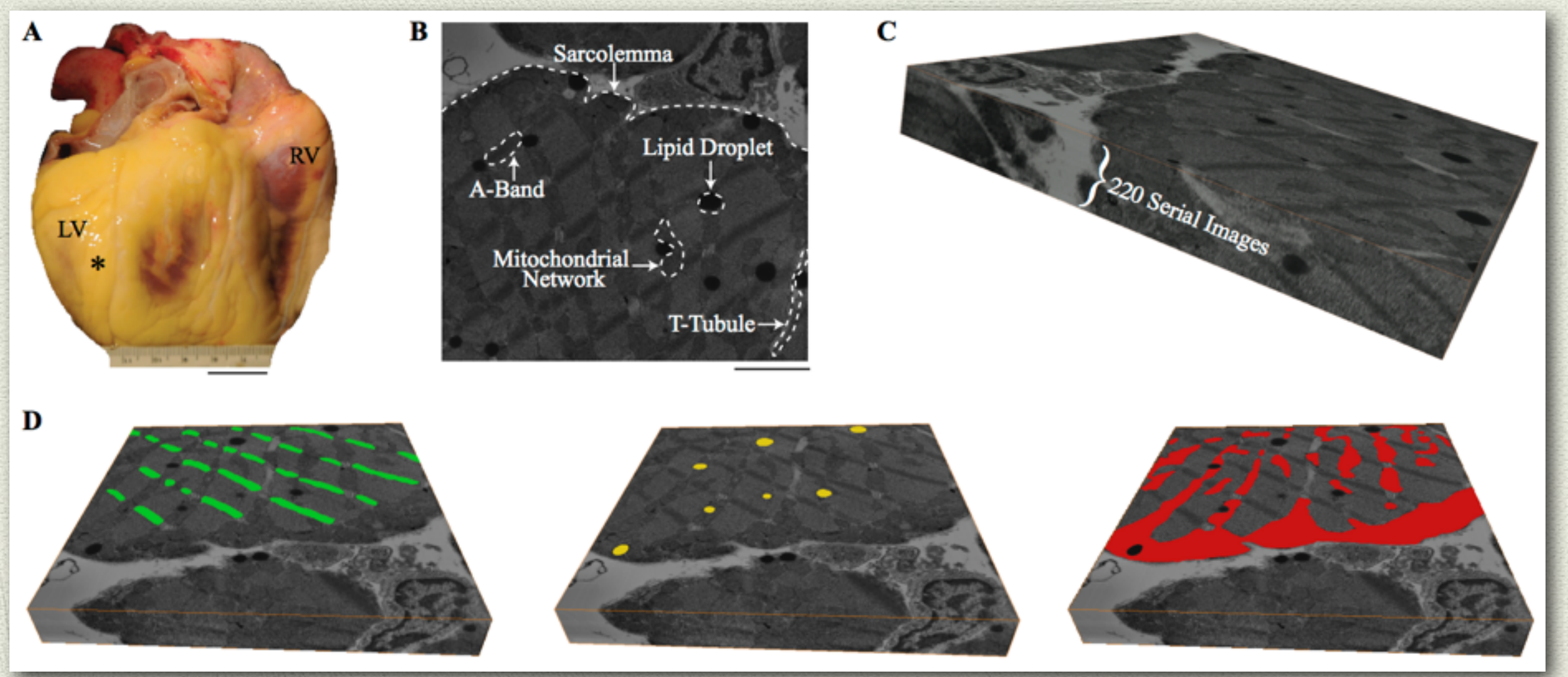
Auto Slice and View G2: Sequential FIB/SEM



L. HOLZER, et al., Journal of Microscopy. 2004. 216 (1): 84–95

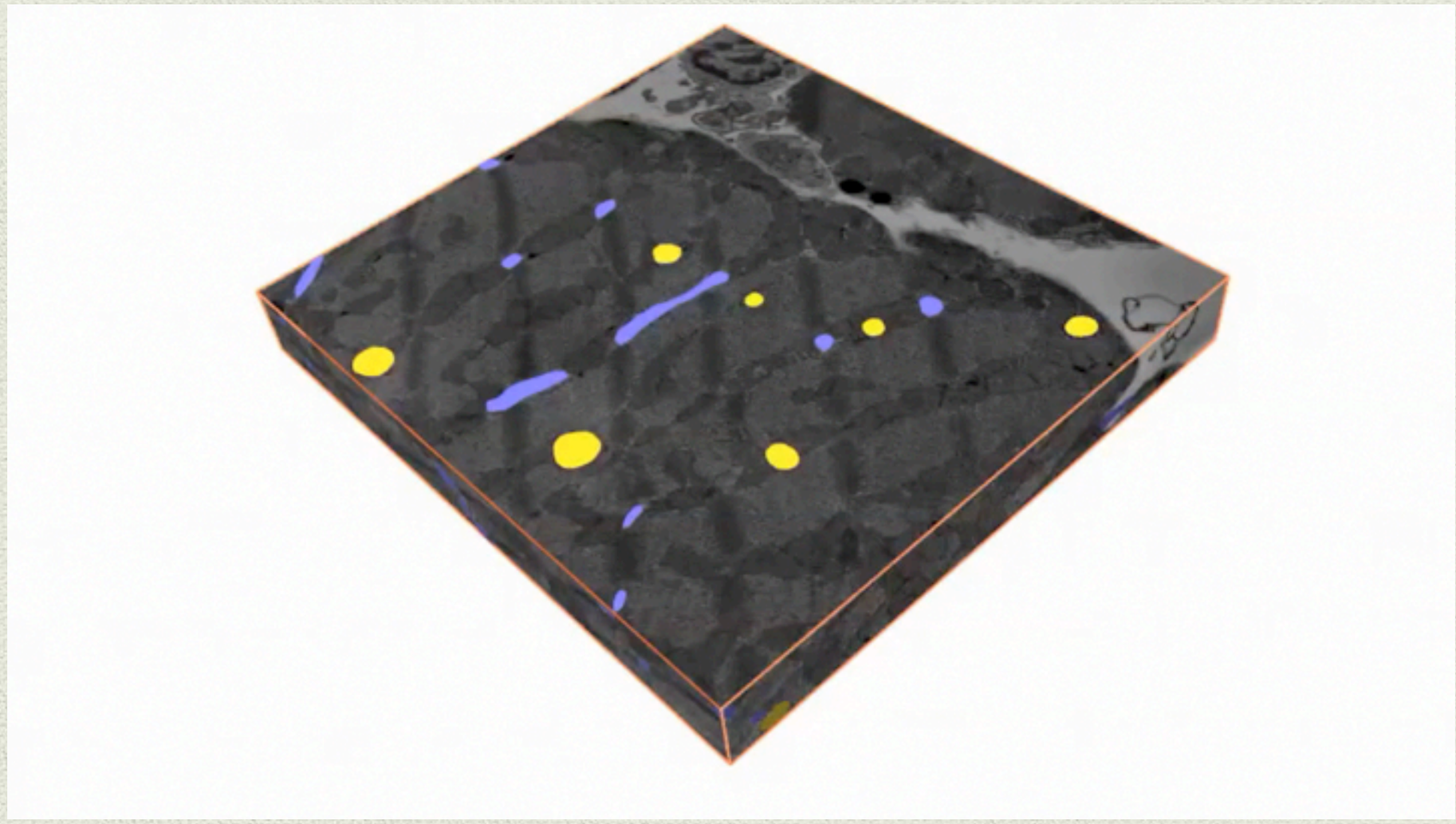


Dual beam imaging of the human ventricular myocyte



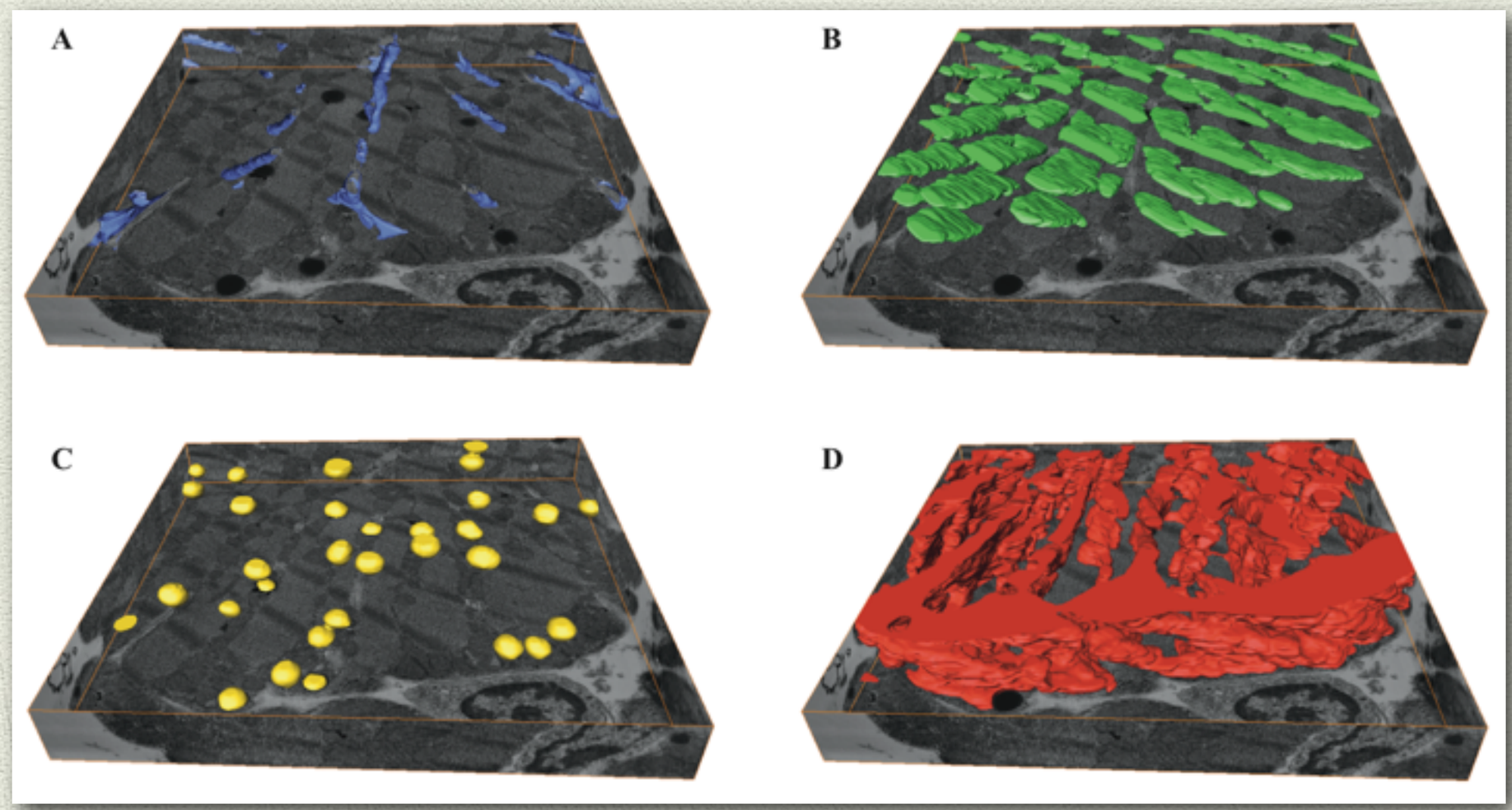
Sulkin, JSB, 2014

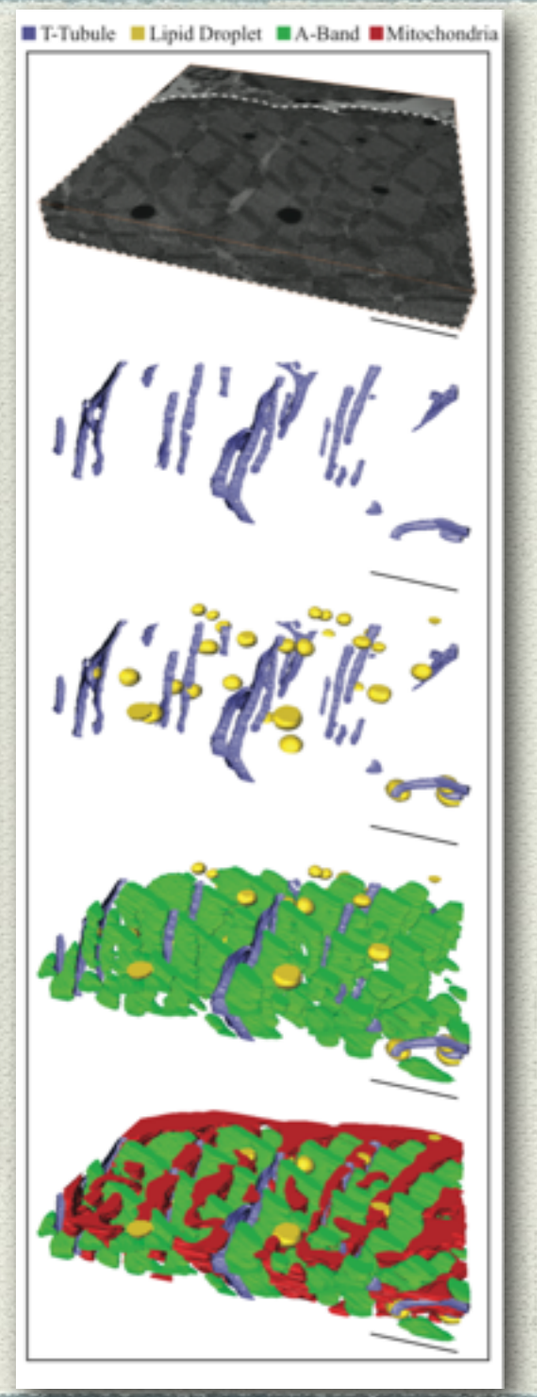
Volume: 15µm x 15µm x 2.2µm,
4096 x 3536 x 220 voxels,
voxel dimension 3.6nm x 4.2nm x 10nm



Sulkin, JSB, 2014

Compact packing of sarcollemal components: lipid droplets co-localization with T-tubules





Sulkin, JSB, 2014

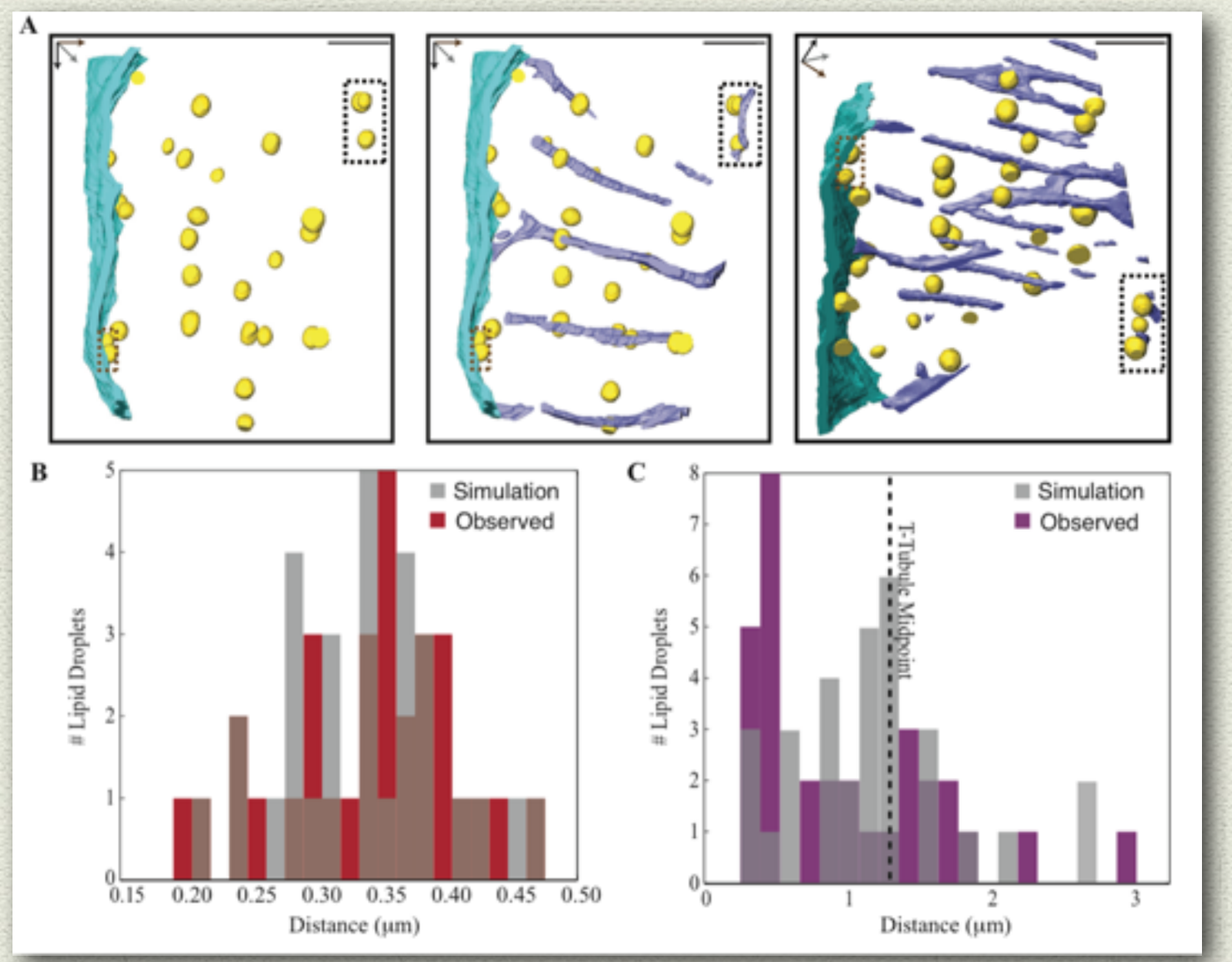
Metabolic synchronization and JIT delivery of substrates via T-tubules

- T-tubules serve as delivery tunnels for fatty acid and carbohydrate metabolic substrate delivery to the intracellular utilization targets (sarcomeric mitochondria)

- T-tubules shorten diffusion length of fatty acids and glucose from sarcolemma to sarcomeric mitochondria thus synchronizing metabolic substrate delivery to sarcomeres

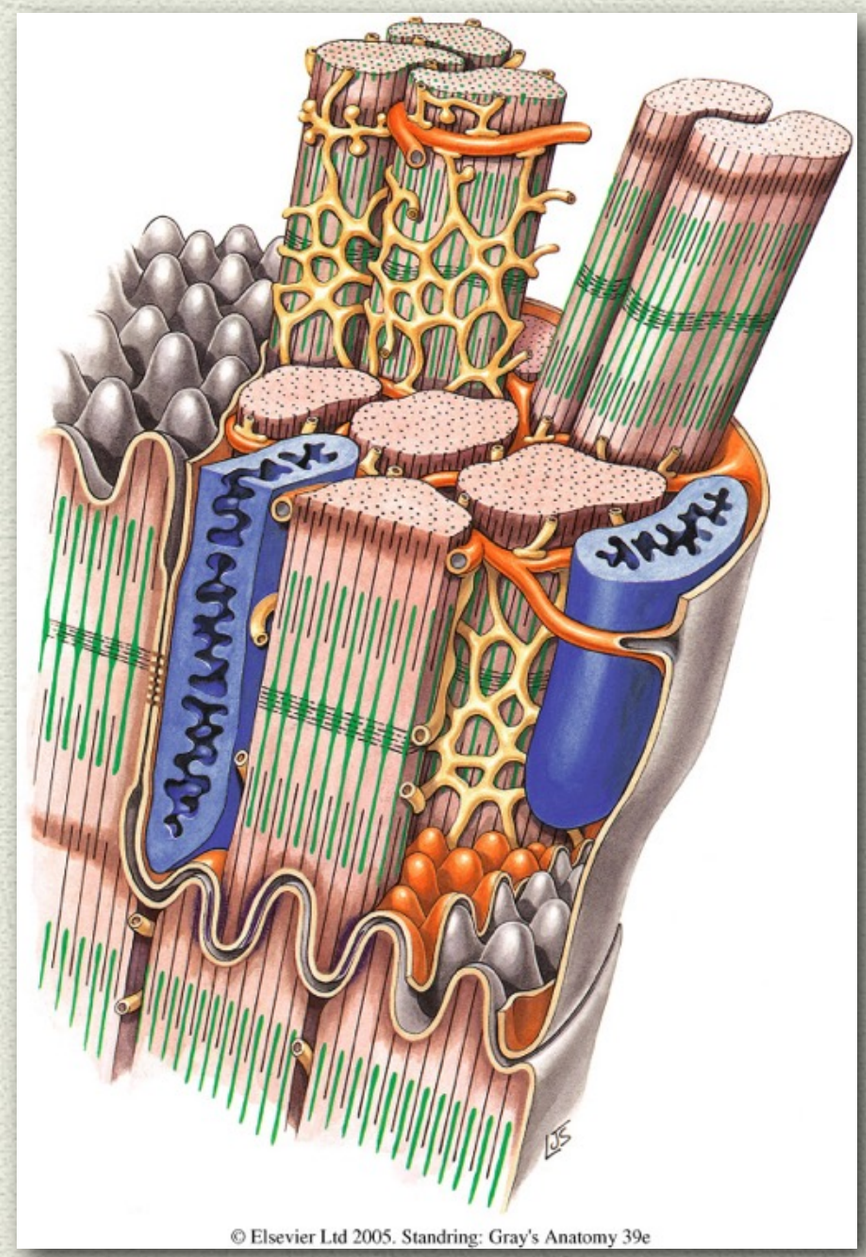
- Detubulation in HF leads to asynchronous substrate delivery and excitation-contraction coupling and necessitates reliance on subsarcolemmal mitochondria and leading to the need for long distance diffusion of ATP

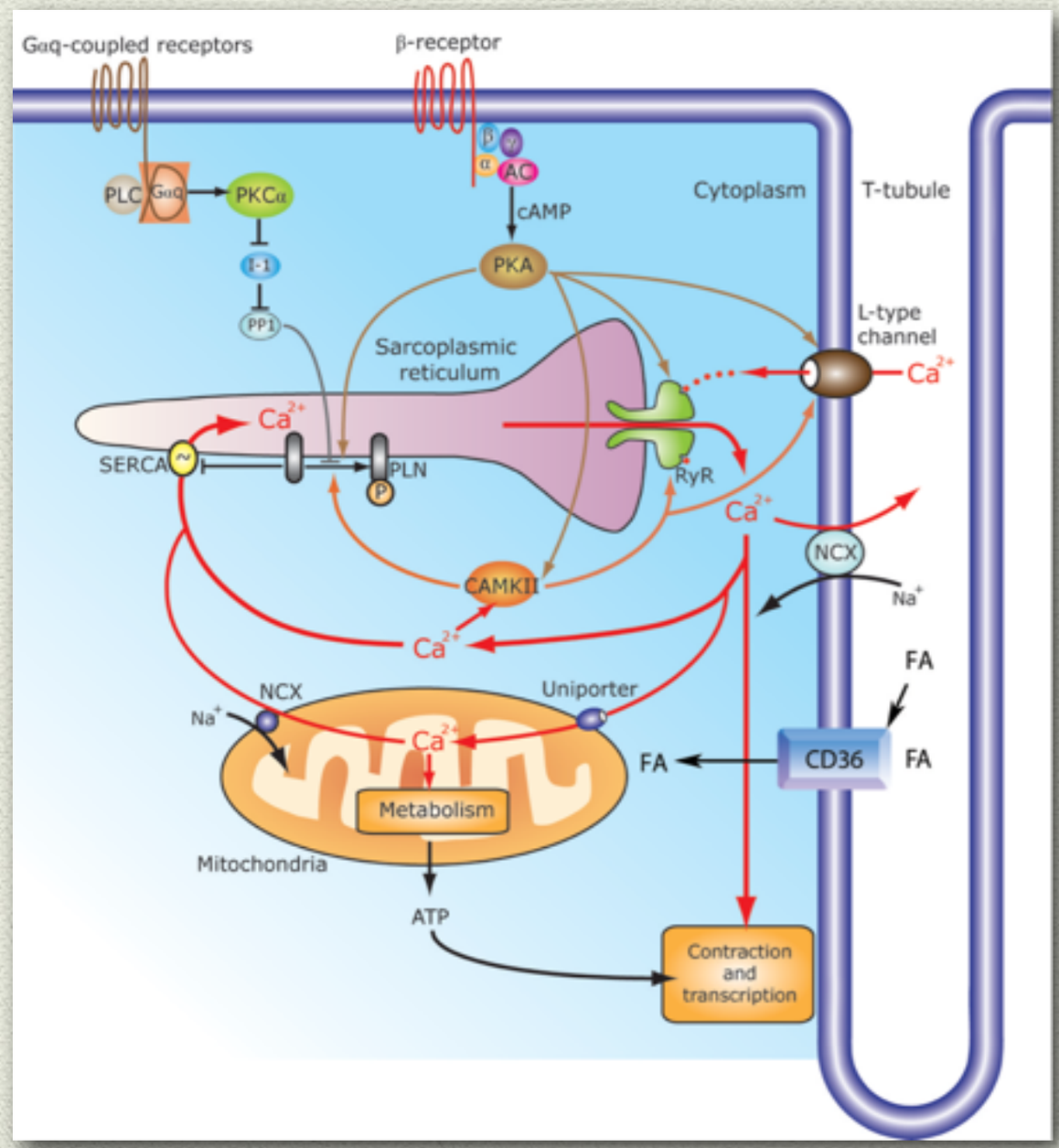
Sulkin, JSB, 2014



B. Distribution plot of the distance from lipid droplet centroids to nearest mitochondria.
C. Distribution plot of the distance from lipid droplet centroids to nearest t-tubule vs. random distribution of lipid droplets.

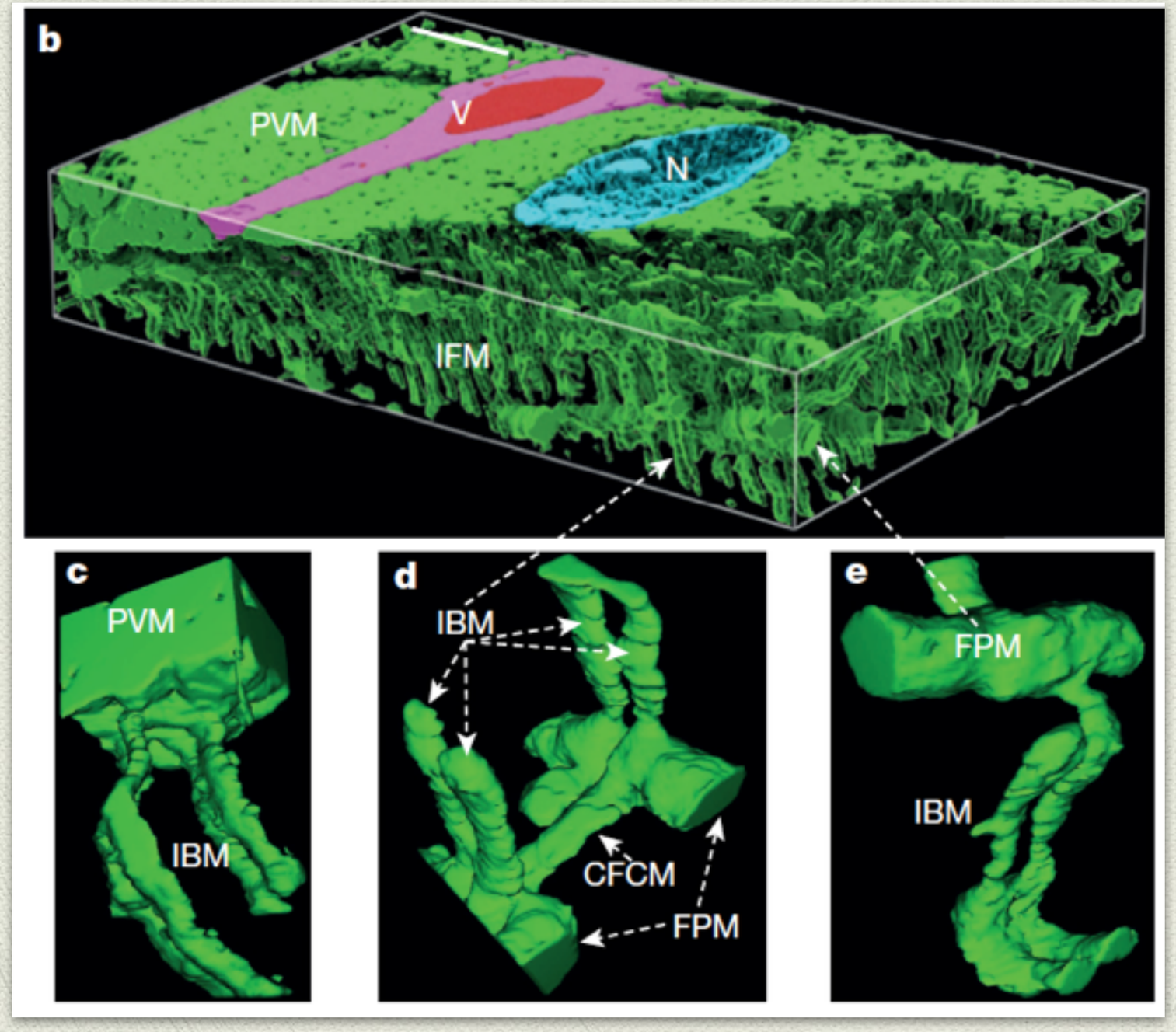
Intact T-tubular system synchronizes Metabolism-excitation-contraction





Sulkin, JSB, 2014

Glancy-Balaban: Muscle Mitochondria Form Highly Connected Functional Networks

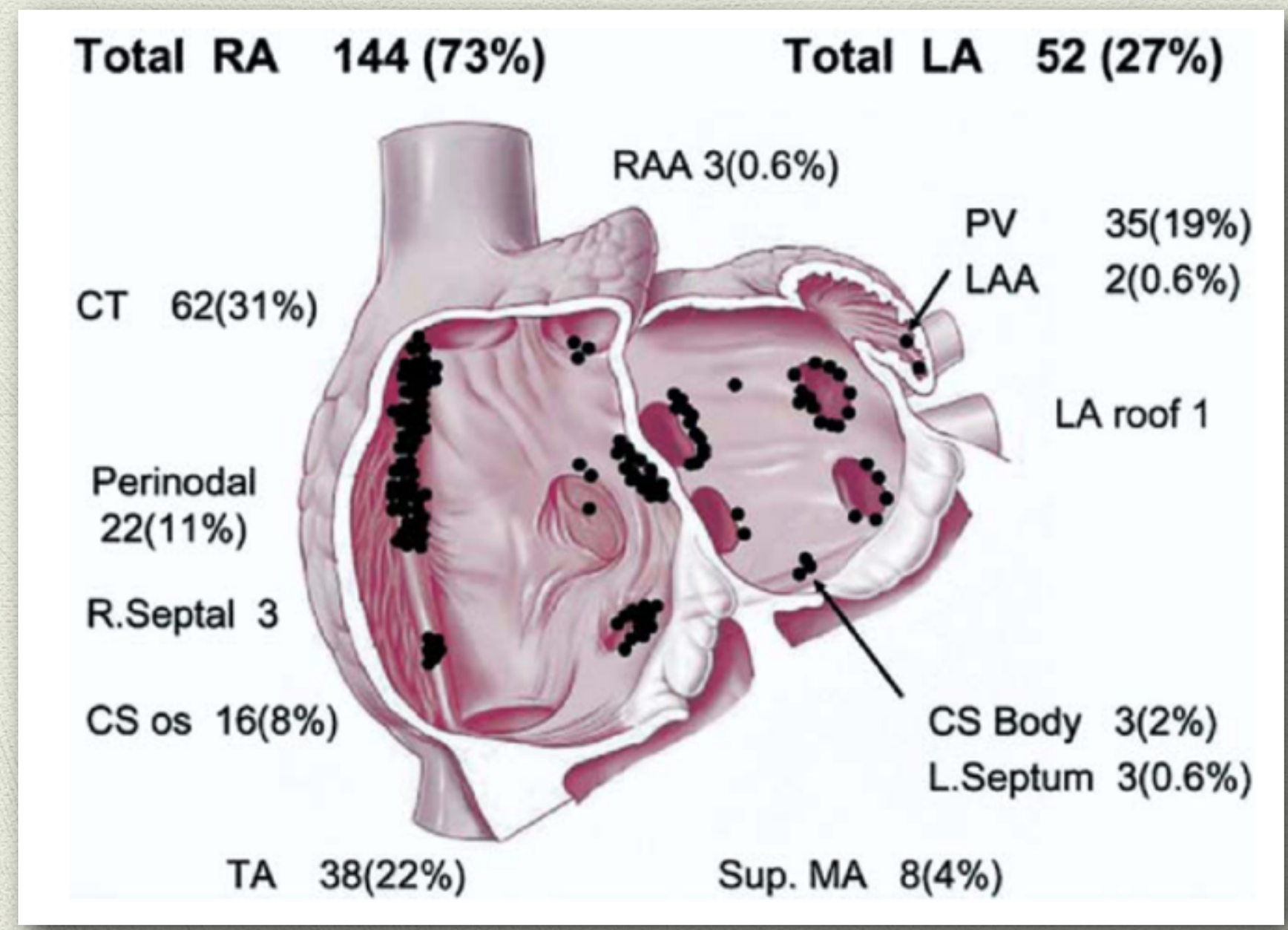


Clancy et al., Mitochondrial reticulum for cellular energy distribution in muscle. Nature, 2015.

Outline

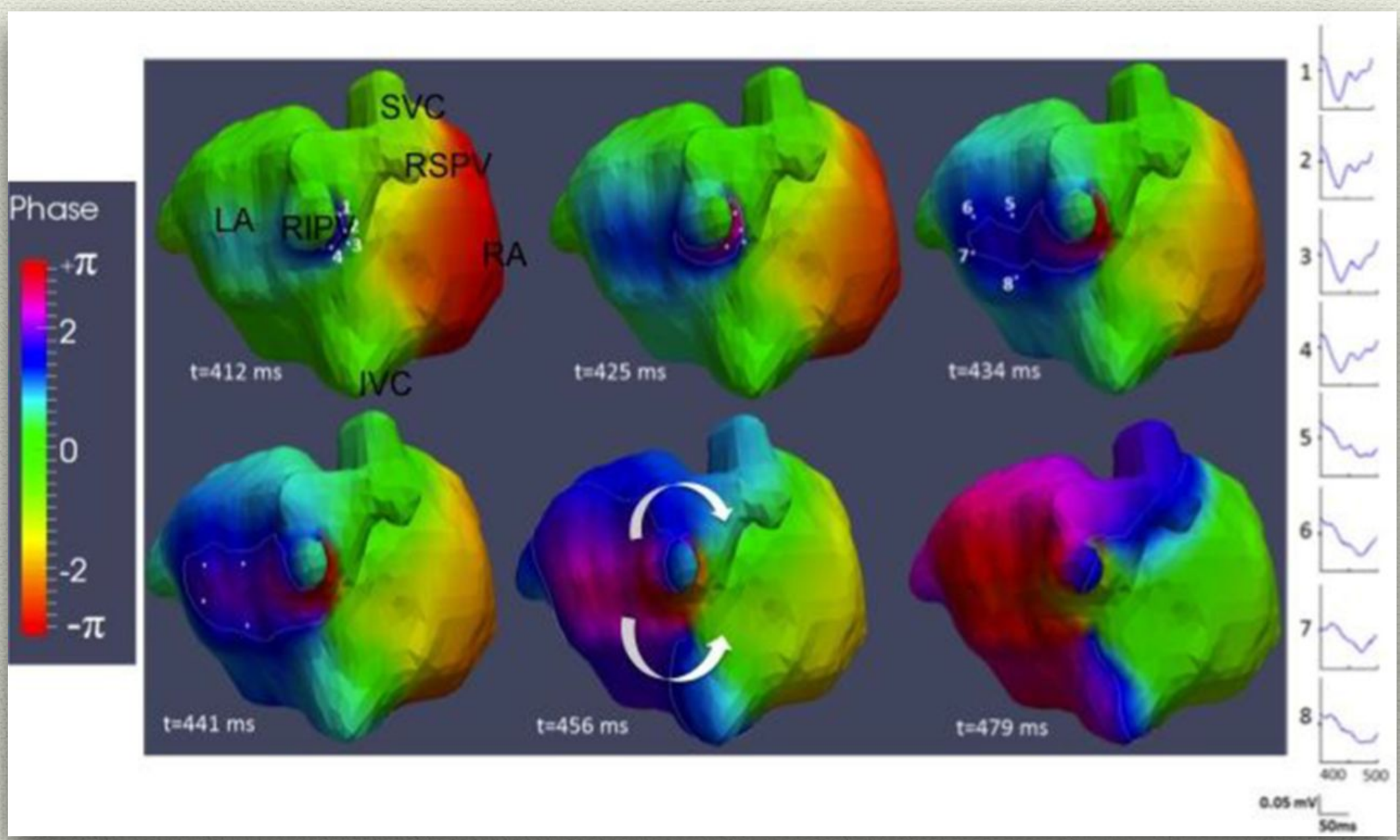
- Need for studying human physiology
- Electrophysiology remodeling
- Metabolic remodeling
- Adrenergic remodeling
- New methodology

Sources of Atrial Tachycardia and Fibrillation: Target for High-definition Mapping and Ablation



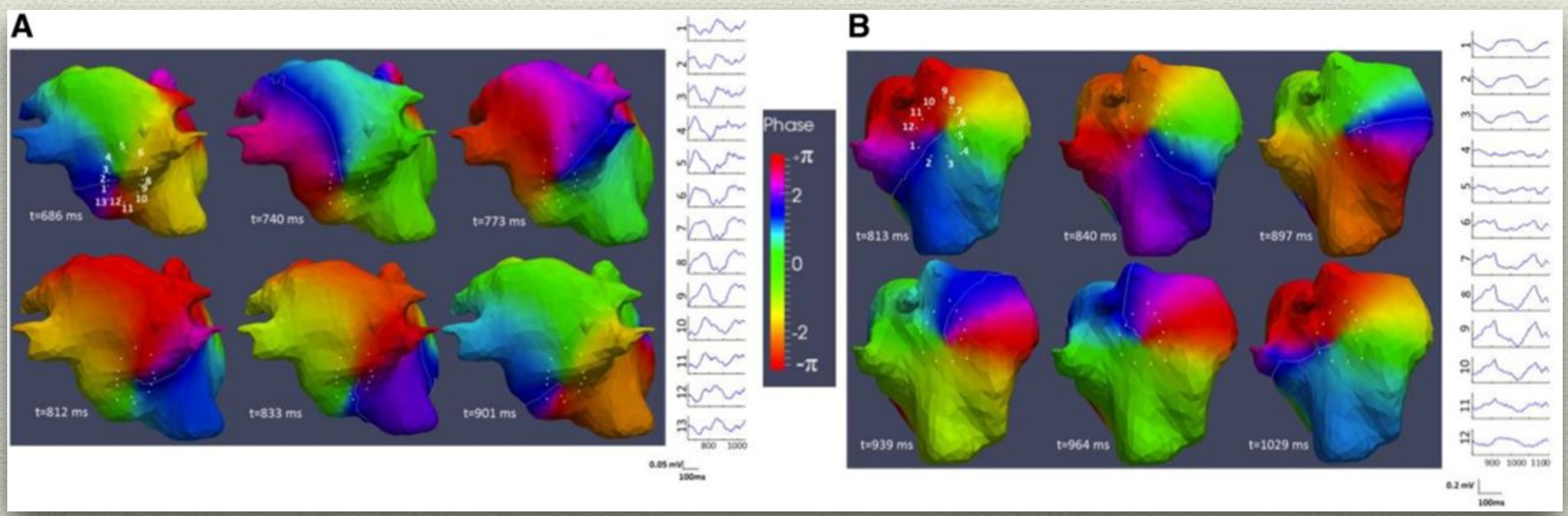
Kistler et al. P-Wave Morphology in Focal Atrial Tachycardia. J Am Coll Cardiol 2006;48:1010 -7.

The phase map shows a focal source that emanates an impulse from the RIPV and initiates a couple of reentrant drivers.



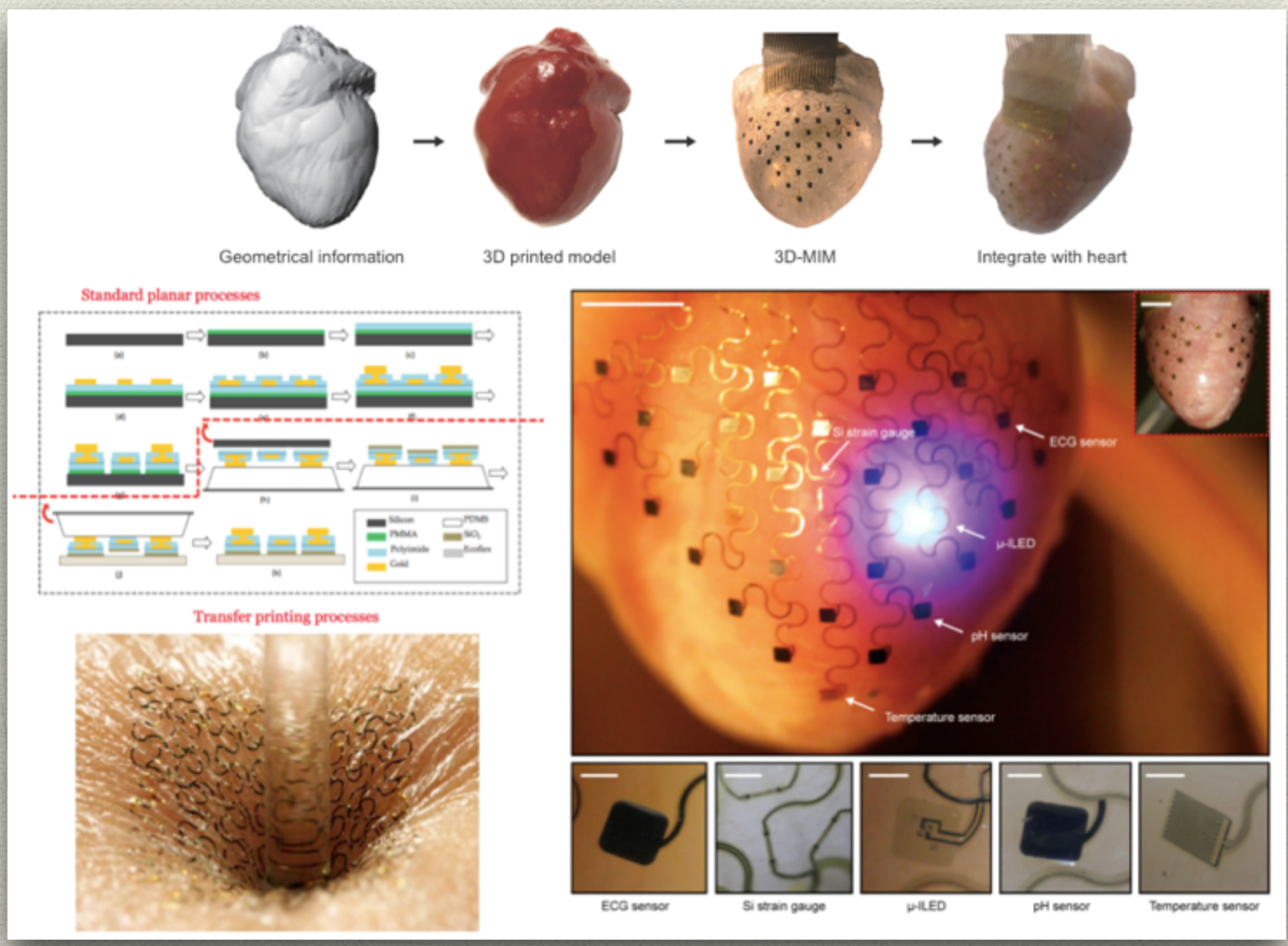
Haissaguerre M et al. Circulation. 2014;130:530-538

The phase maps of ≥1000-ms-long AF window show reentry events visualized intermittently in the right and left atria with their prephase electrograms on the right.



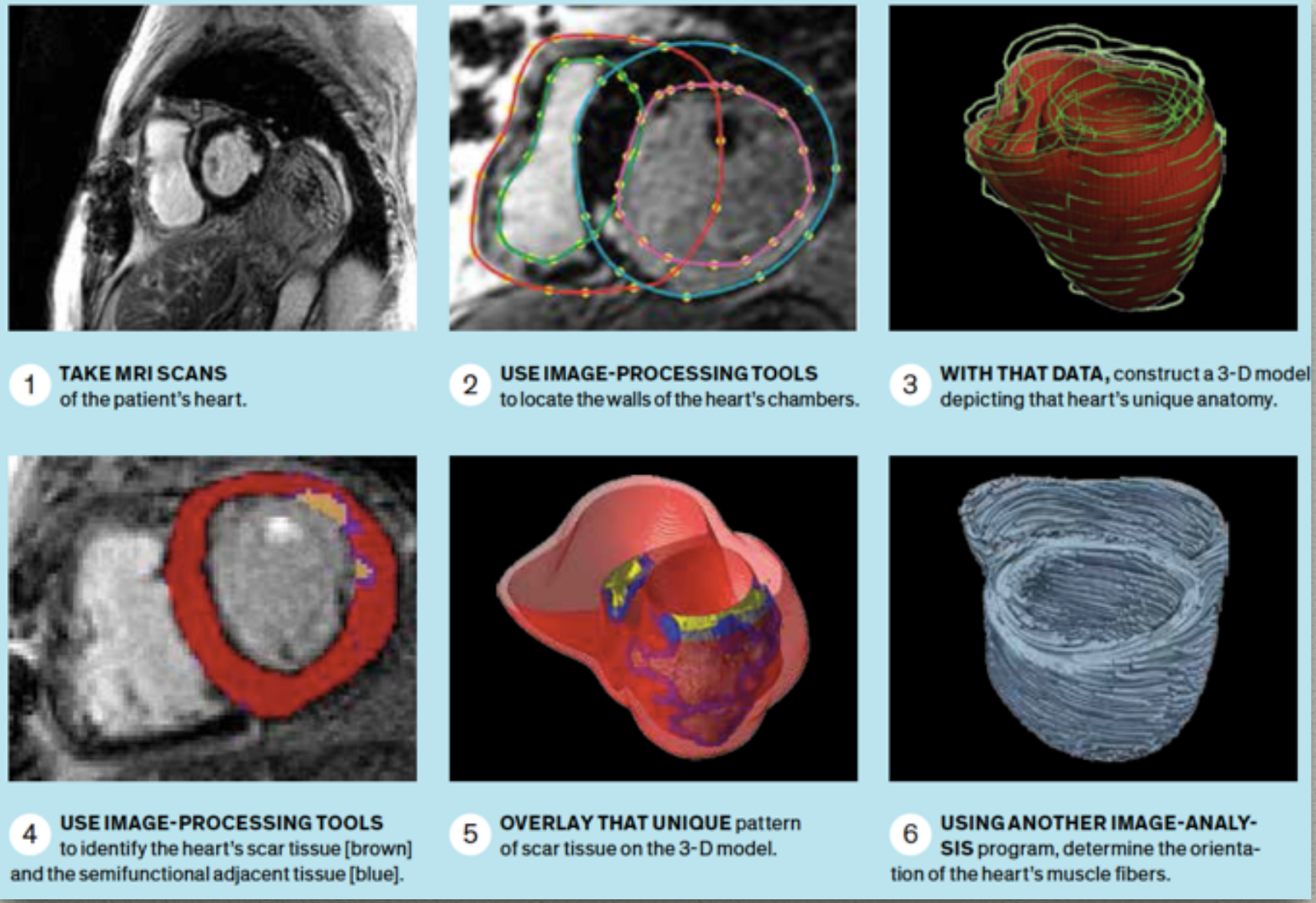
Haissaguerre M et al. Circulation. 2014;130:530-538

3D Multifunctional Integumentary Membranes (3D-MIMs) for high-density cardiac mapping and stimulation



Xu et al, Nature Communication, 2014

Patient-specific heart anatomy: Making the Mock-Up



1 **TAKE MRI SCANS** of the patient's heart.

2 **USE IMAGE-PROCESSING TOOLS** to locate the walls of the heart's chambers.

3 **WITH THAT DATA,** construct a 3-D model depicting that heart's unique anatomy.

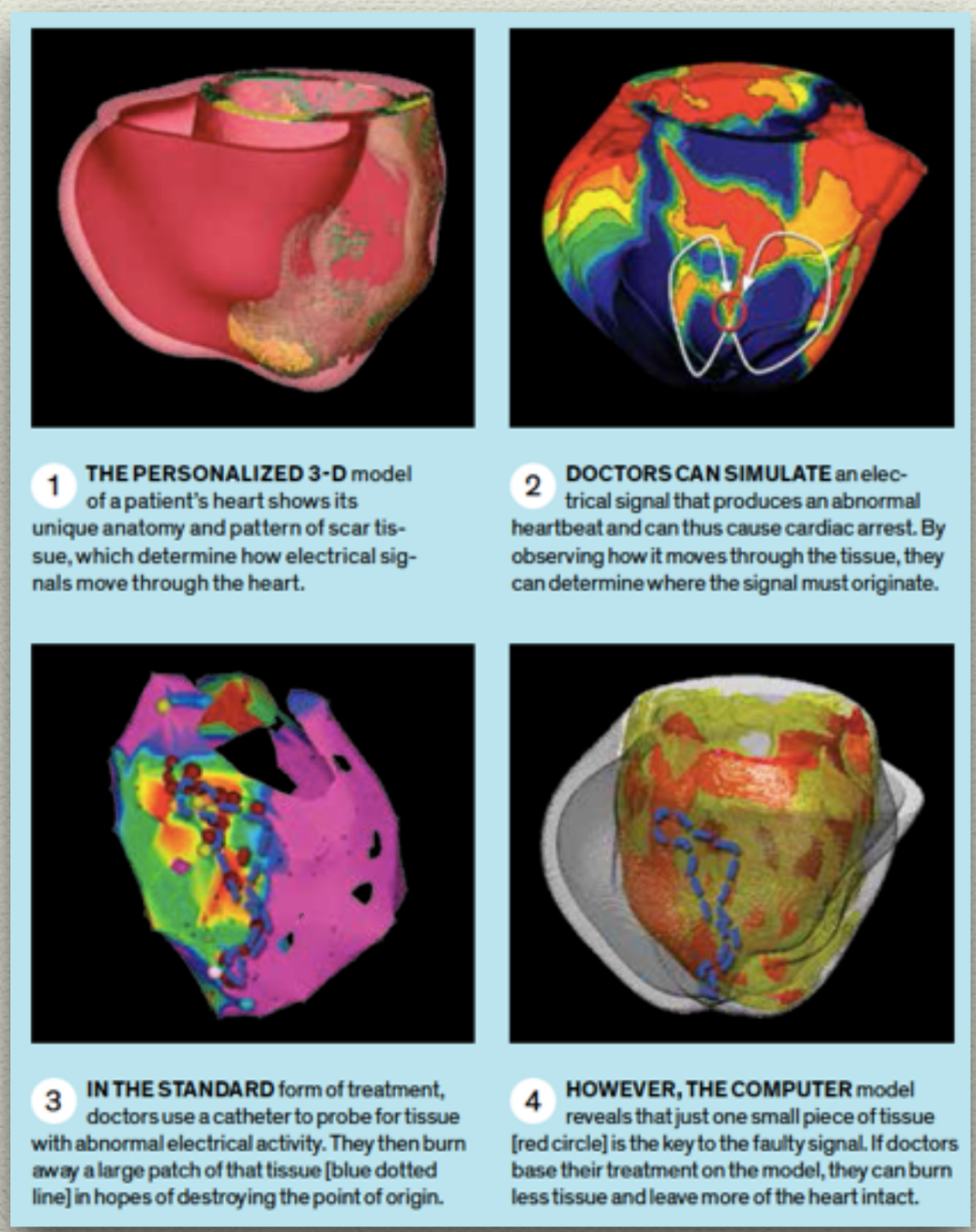
4 **USE IMAGE-PROCESSING TOOLS** to identify the heart's scar tissue [brown] and the semifunctional adjacent tissue [blue].

5 **OVERLAY THAT UNIQUE** pattern of scar tissue on the 3-D model.

6 **USING ANOTHER IMAGE-ANALYSIS** program, determine the orientation of the heart's muscle fibers.

Trayanova NA, IEEE Spectrum, 2014

Patient-specific heart anatomy: Identifying the Problem



1 **THE PERSONALIZED 3-D** model of a patient's heart shows its unique anatomy and pattern of scar tissue, which determine how electrical signals move through the heart.

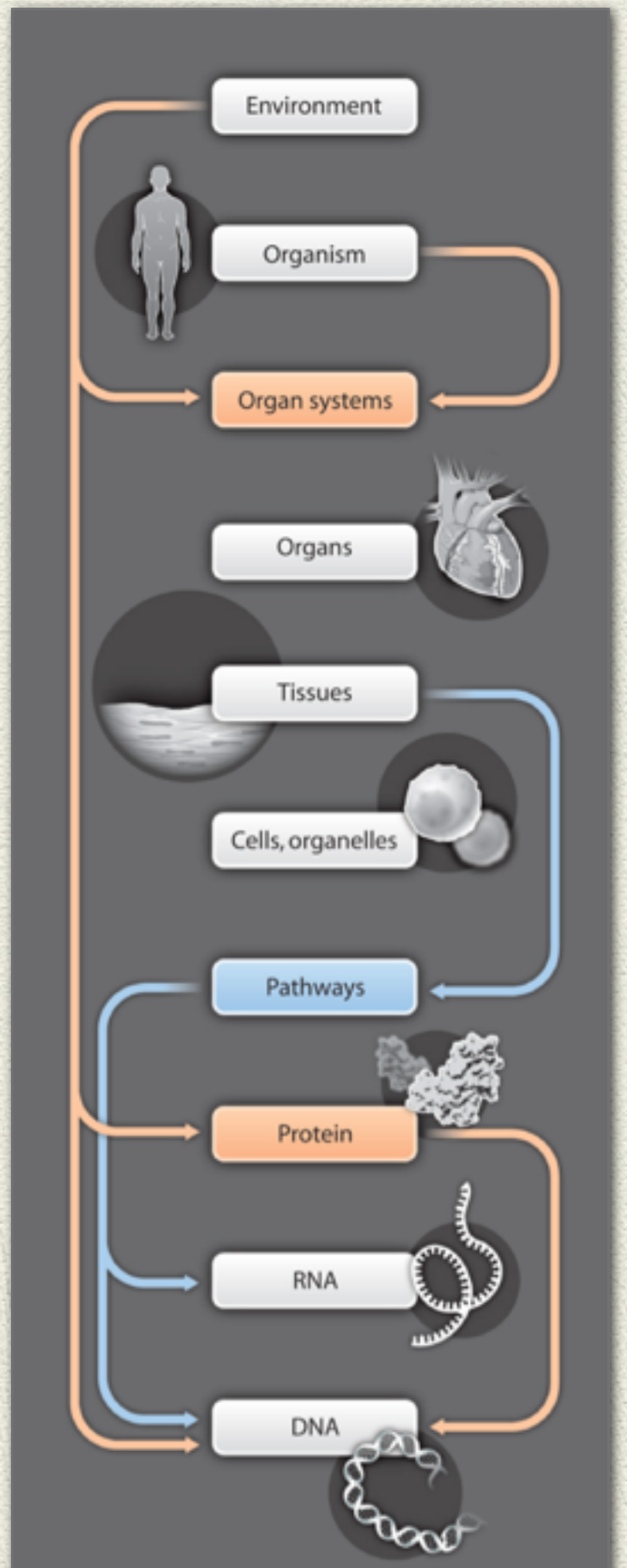
2 **DOCTORS CAN SIMULATE** an electrical signal that produces an abnormal heartbeat and can thus cause cardiac arrest. By observing how it moves through the tissue, they can determine where the signal must originate.

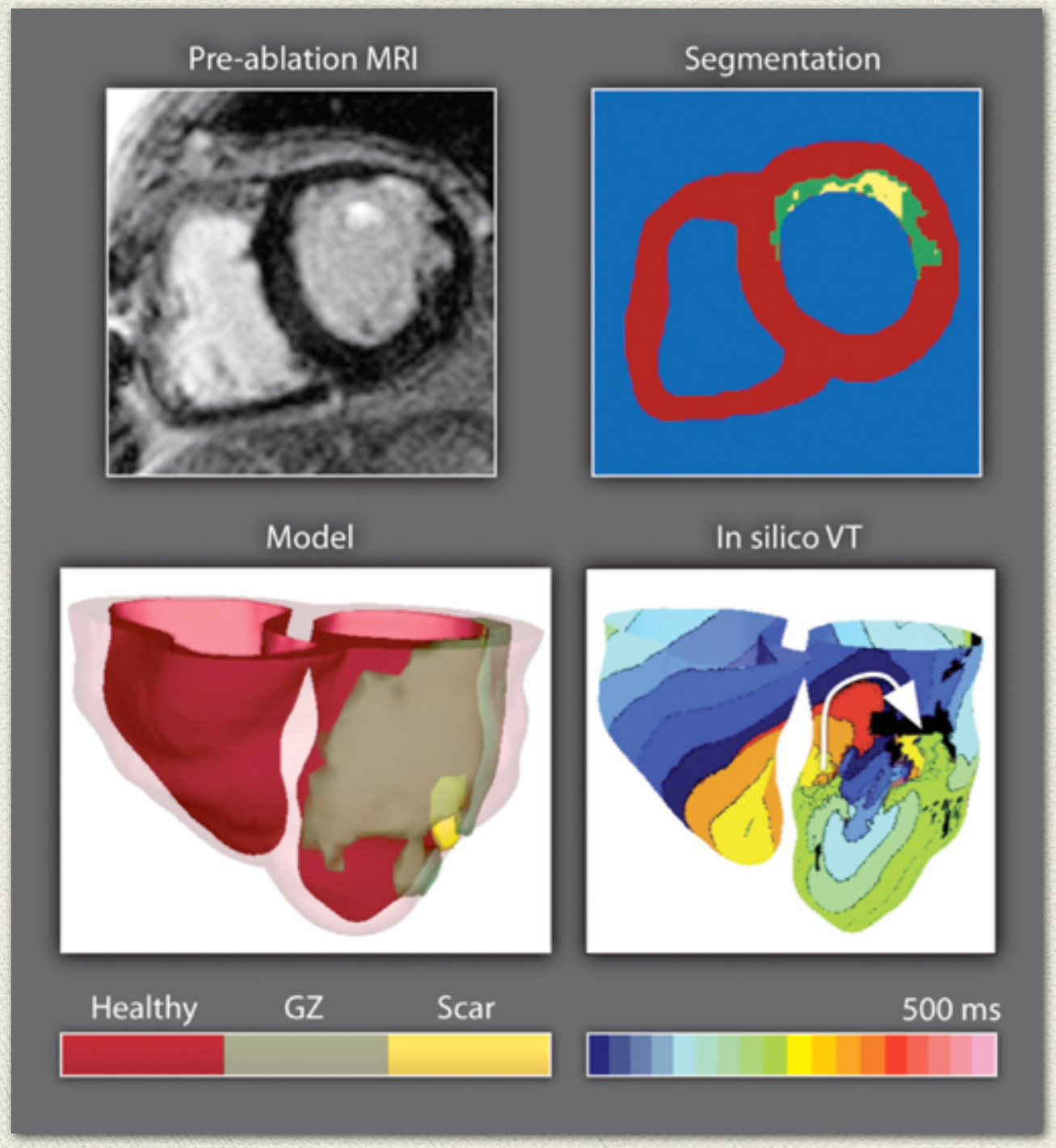
3 **IN THE STANDARD** form of treatment, doctors use a catheter to probe for tissue with abnormal electrical activity. They then burn away a large patch of that tissue [blue dotted line] in hopes of destroying the point of origin.

4 **HOWEVER, THE COMPUTER** model reveals that just one small piece of tissue [red circle] is the key to the faulty signal. If doctors base their treatment on the model, they can burn less tissue and leave more of the heart intact.

Trayanova NA, IEEE Spectrum, 2014

Multiscale Modeling





Winslow et al, 2012

Conclusions

- Animal models are critically important for producing basic physiological knowledge.
- Findings in animal models of heart diseases have low likelihood of translation to the bedside.
- We found important differences between human and animal models' physiology.
- Human heart research is needed for translation of basic findings to clinic.

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Collaborators:

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- Natalia A. Trayanova, Johns Hopkins University, Baltimore, MD
- Yoram Rudy, Washington University in St. Louis, MO

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- The Alisann & Terry Collins Endowment, The George Washington University


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