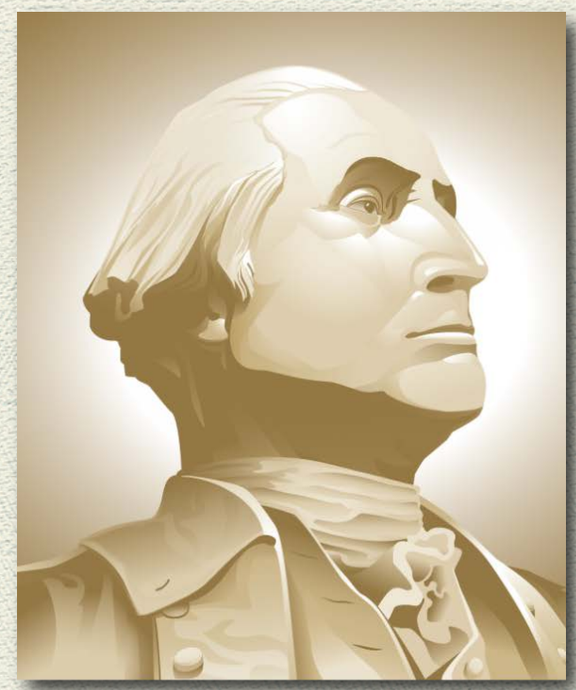


THE GEORGE WASHINGTON UNIVERSITY

WASHINGTON, DC

Innovation in Biomedical Engineering Industry:

A Vision for the Future and how to be a part of it

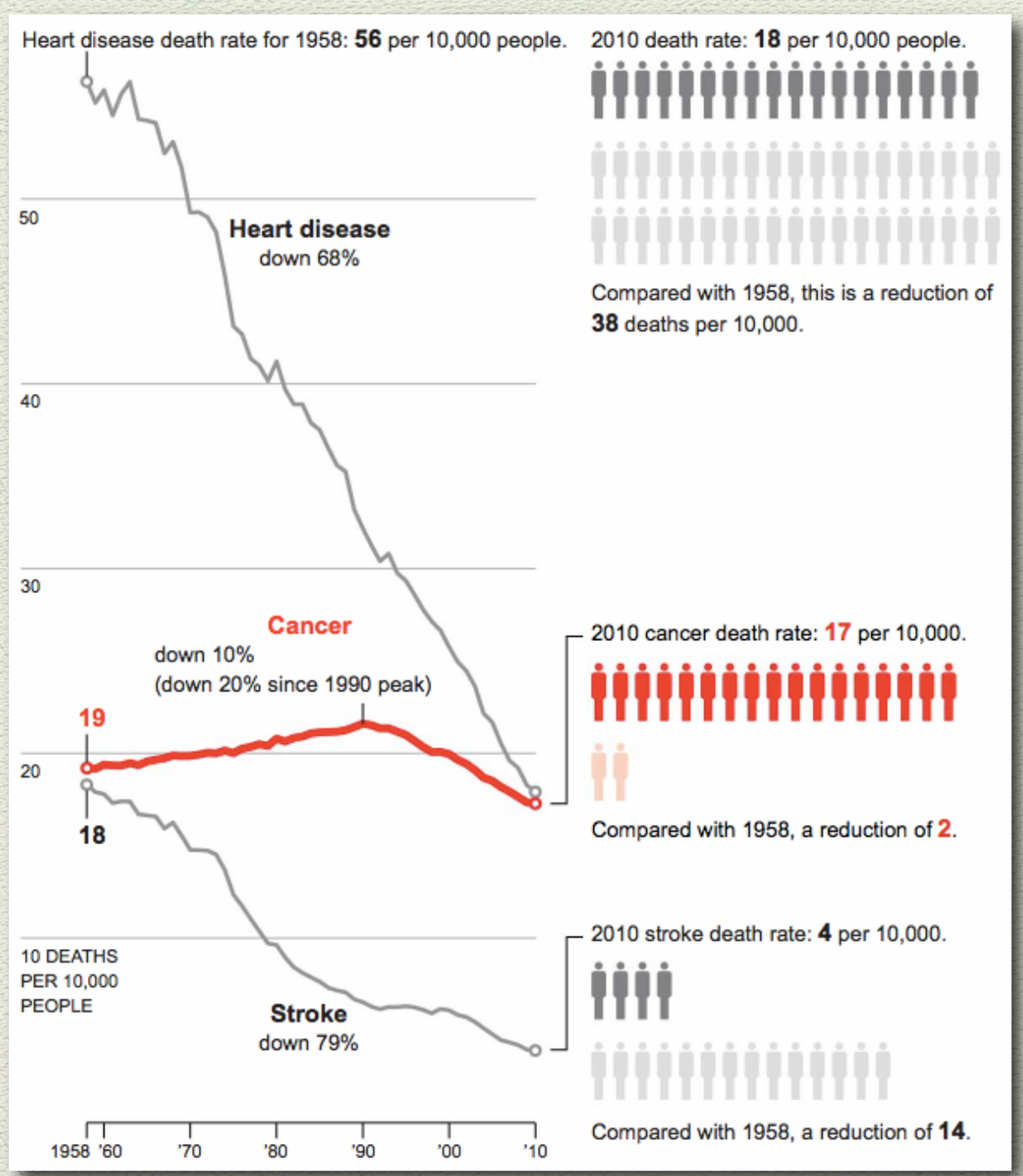
Igor R. Efimov, Ph.D., F.A.I.M.B.E., F.A.H.A., F.H.R.S.

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

Result of Biomedical Innovation

The Rise of Life Expectancy in the USA (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



New York Times, Jan 4, 2014

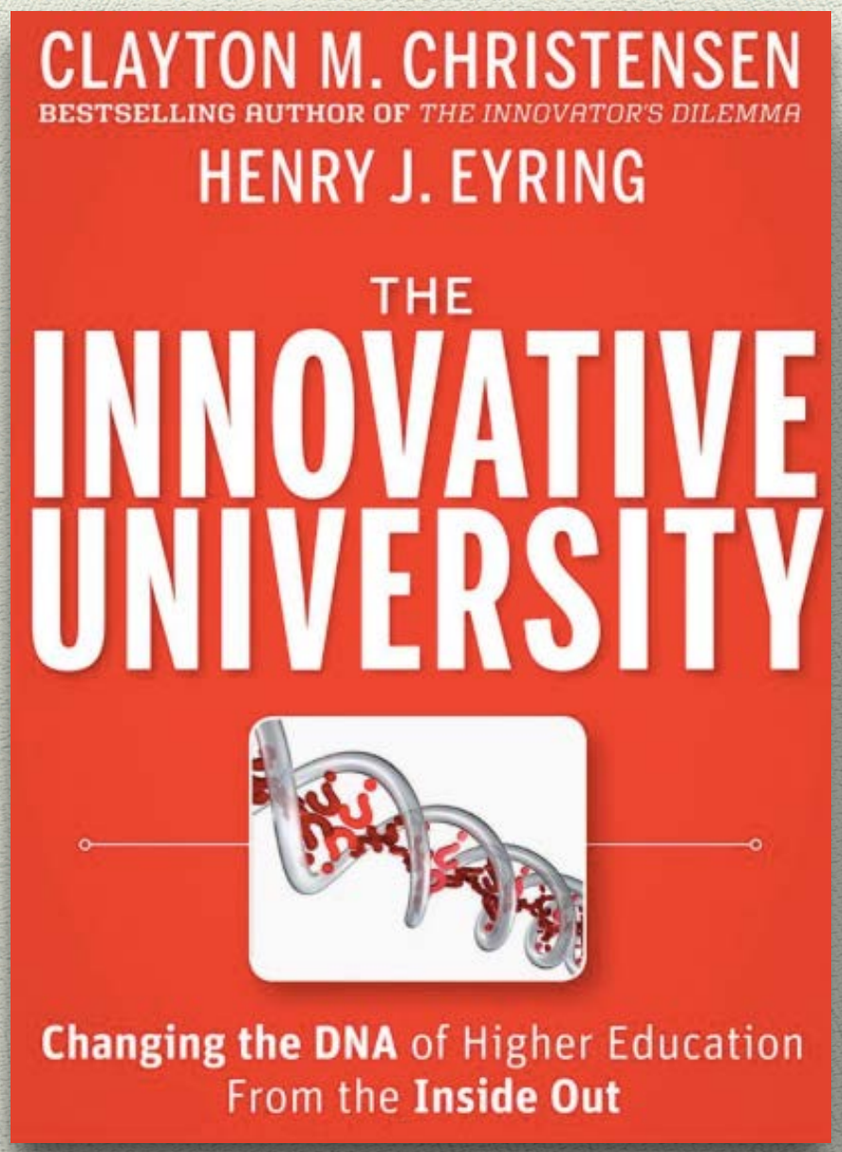
Outline

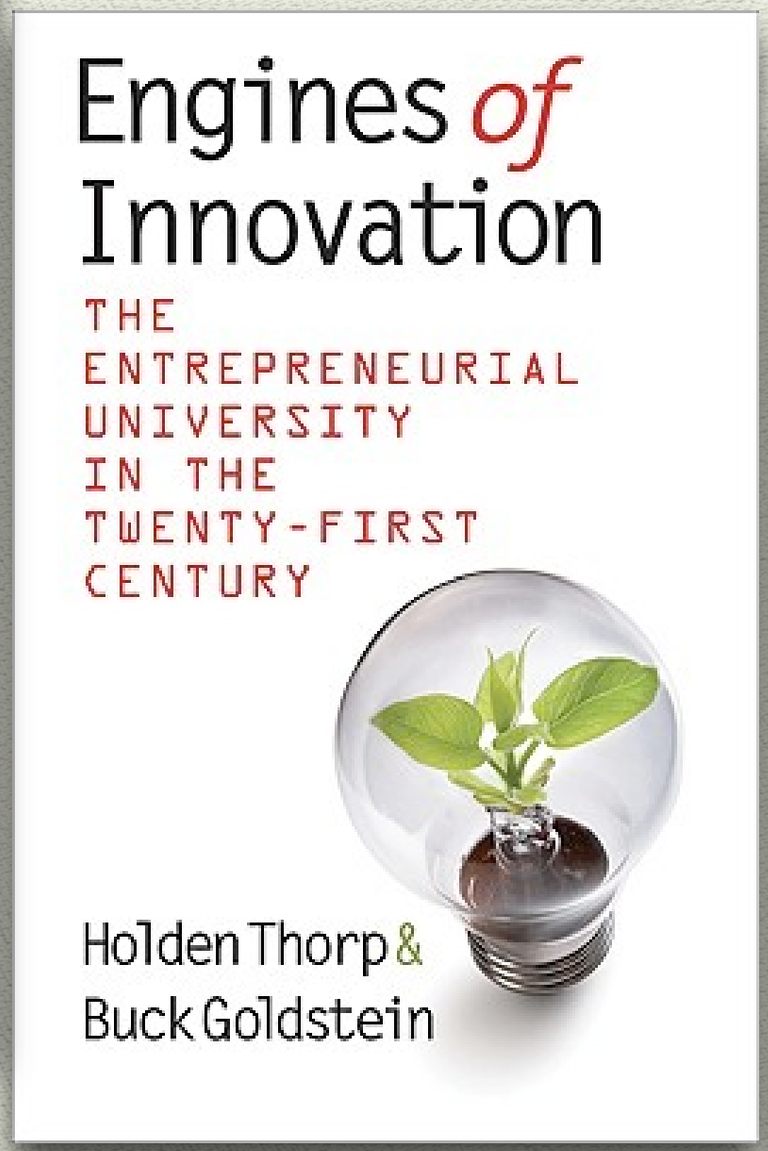
- Engines of Innovation: Innovative University
- Biomedical Research Enterprise
- Therapy for Cardiac Arrhythmias
- Stretchable and flexible electronics
- Patient-specific therapies

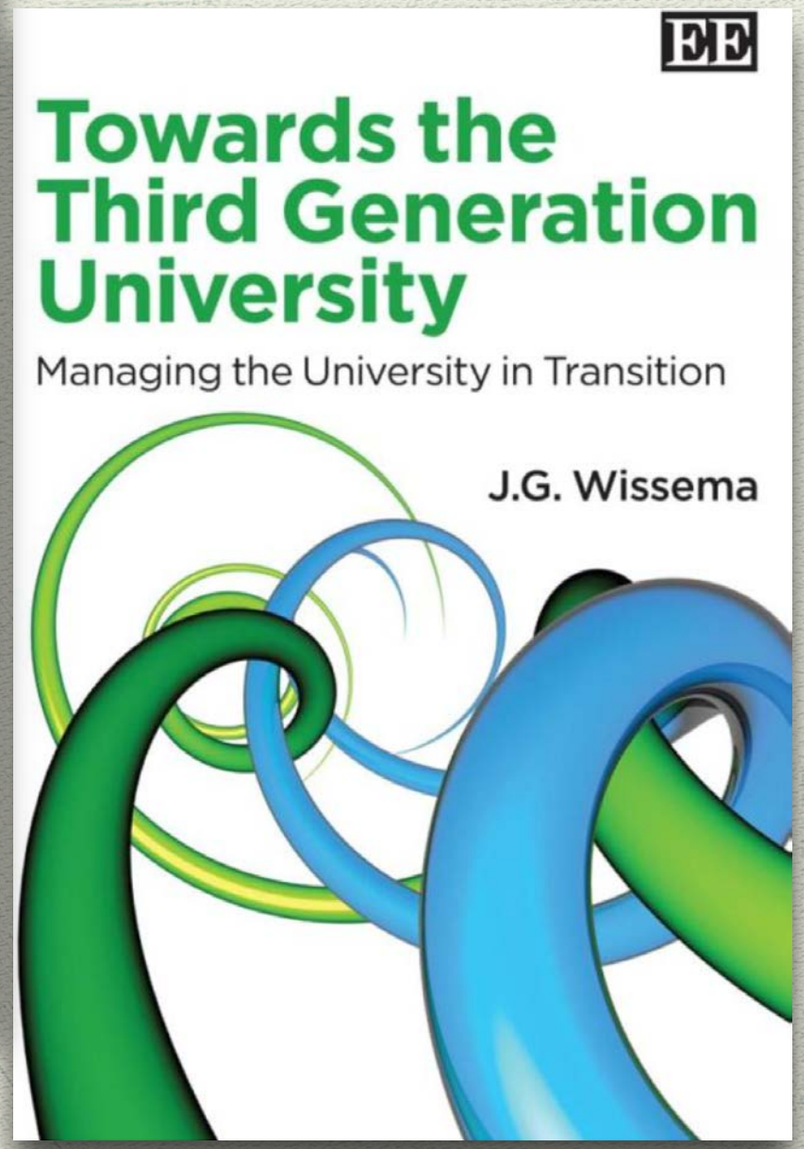
The 20th Century Idea Factory

Big ideas of AT&T (Bell Labs): Telephone, Information theory, Transistor, Space satellites, Cell phone, etc.

The Innovative University: Engine of Innovation







3rd Generation University

1st generation:
Education

2nd generation:
Education
Research

3rd generation:
Education
Research
Entrepreneurship

University of Paris

Humboldt University

Cambridge University

1000 1500 2000

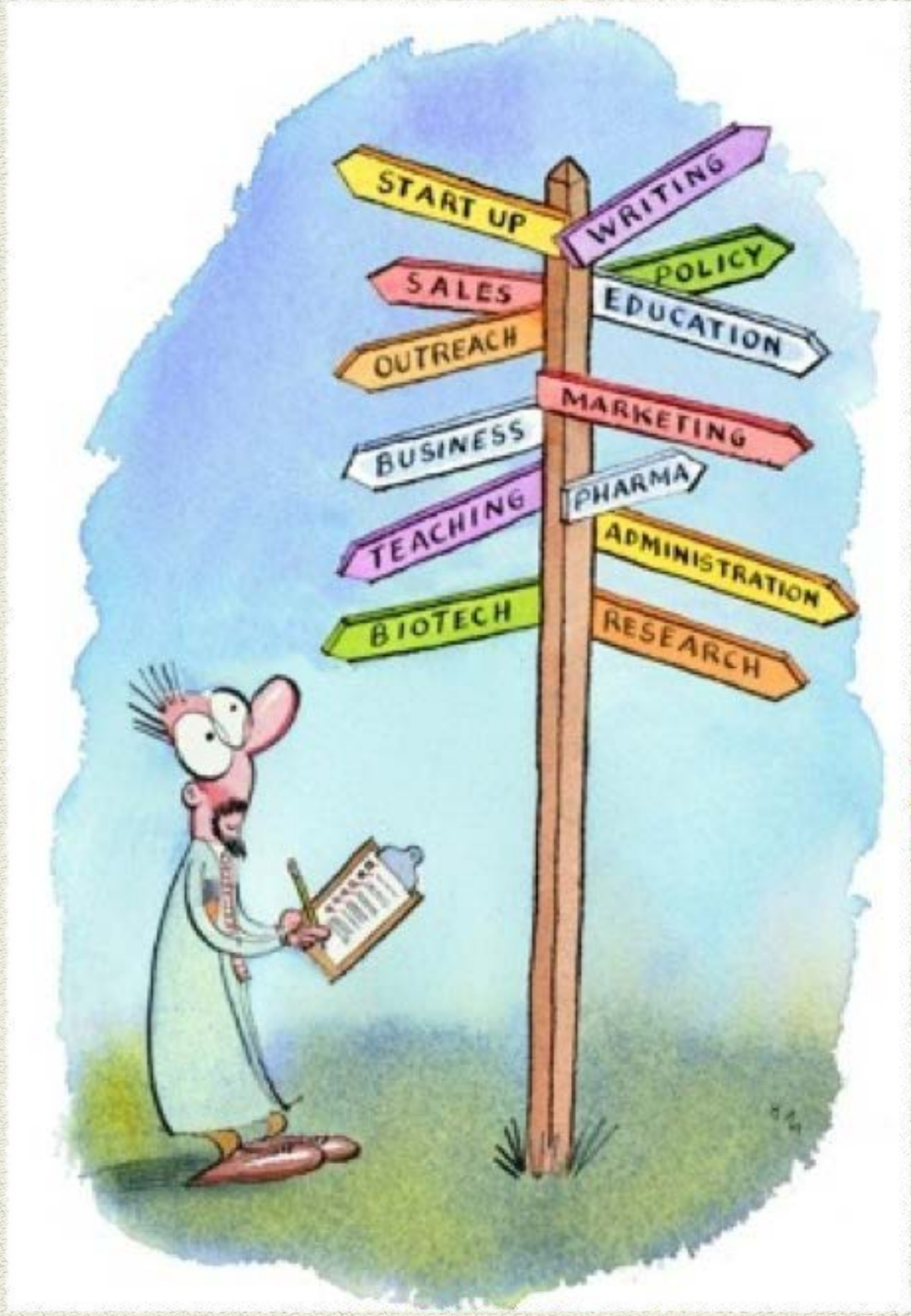
Three Generations of Universities

	1st generation	2nd generation	3rd generation
Objective	Education	Education & research	Education, research & know-how exploitation
Role	Defending the truth	Discovering nature	Creating value
Method	Scholastic	Mono-disciplinary science	Inter-disciplinary science
Human capital development	Professionals	Professionals & scientists	Professionals, scientists & entrepreneurs
Orientation	Universal	National	Global
Language	Latin	National languages	English
Organization	Colleges	Faculties	Institutes & centers
Management	Rector & Chancellor	Part-time academics	Professional management

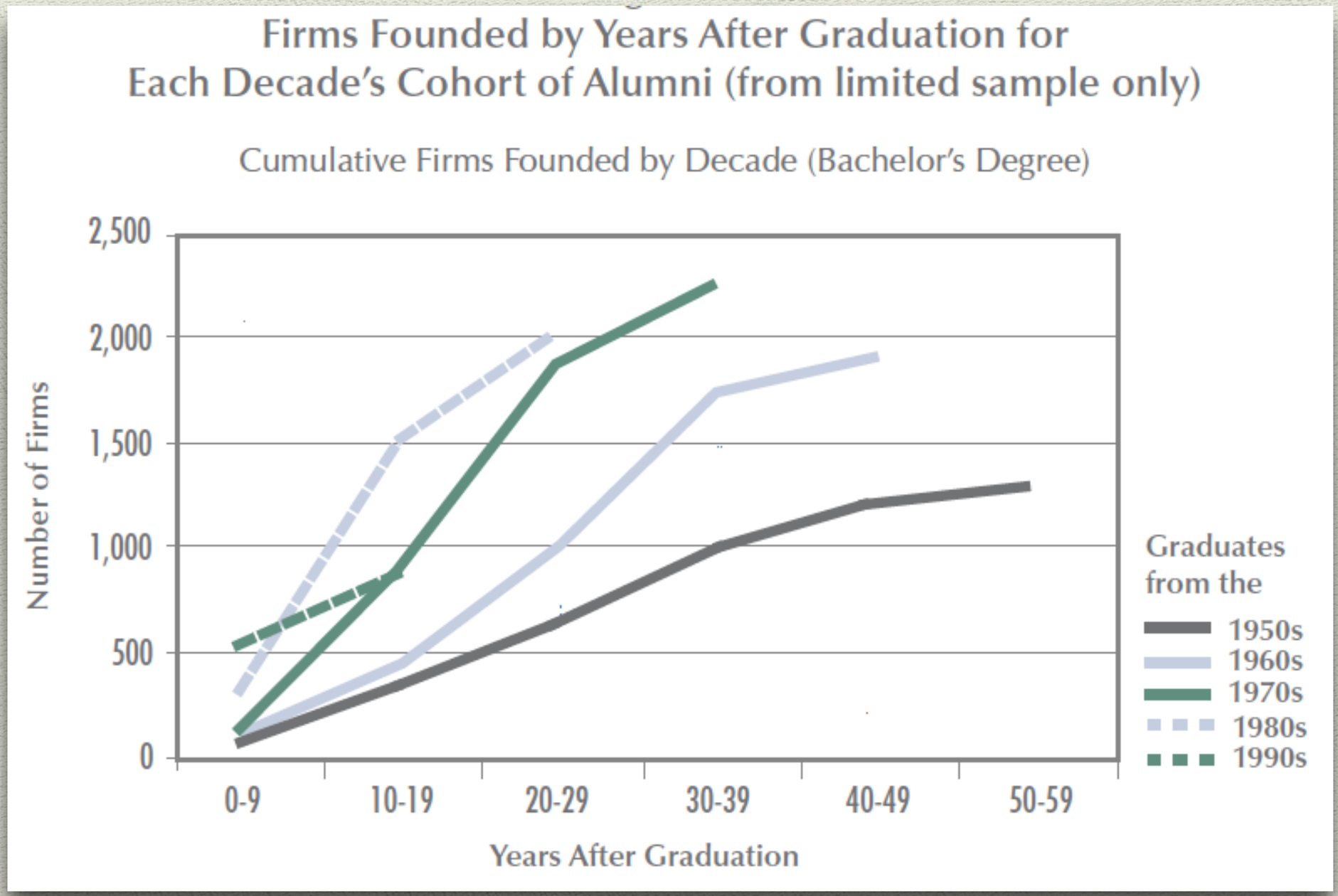
Ph.D. Individual Development Plan:

myidp.sciencecareers.org

- *Principal investigator in a research-intensive institution.*
- *Combined research and teaching careers.*
- *Research in industry.*
- *Clinical practice.*
- *Teaching-intensive careers in academia.*
- *Entrepreneurship.*
- *Sales and marketing of science-related products.*
- *Research staff in a research-intensive institution.*
- *Business of science.*
- *Science policy.*
- *Science education for K-12 schools or non-scientists.*
- *Research administration.*
- *Intellectual property.*
- *Scientific/medical testing.*
- *Science writing.*
- *Clinical research management.*
- *Drug/device approval and production.*
- *Public health related careers.*
- *Support of science-related products*

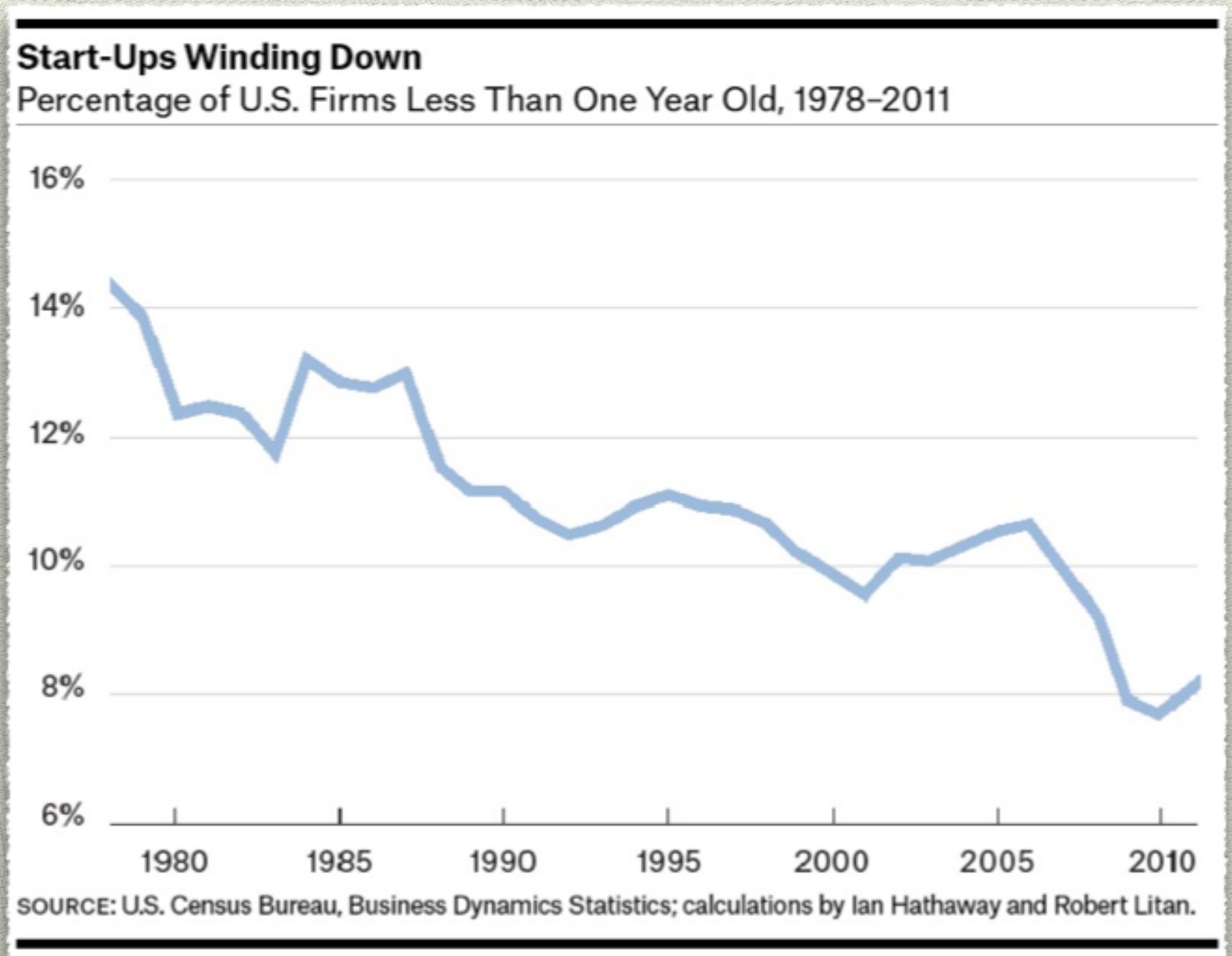


Entrepreneurial Impact: The Role of MIT. Edward B. Roberts & Charles Eesley



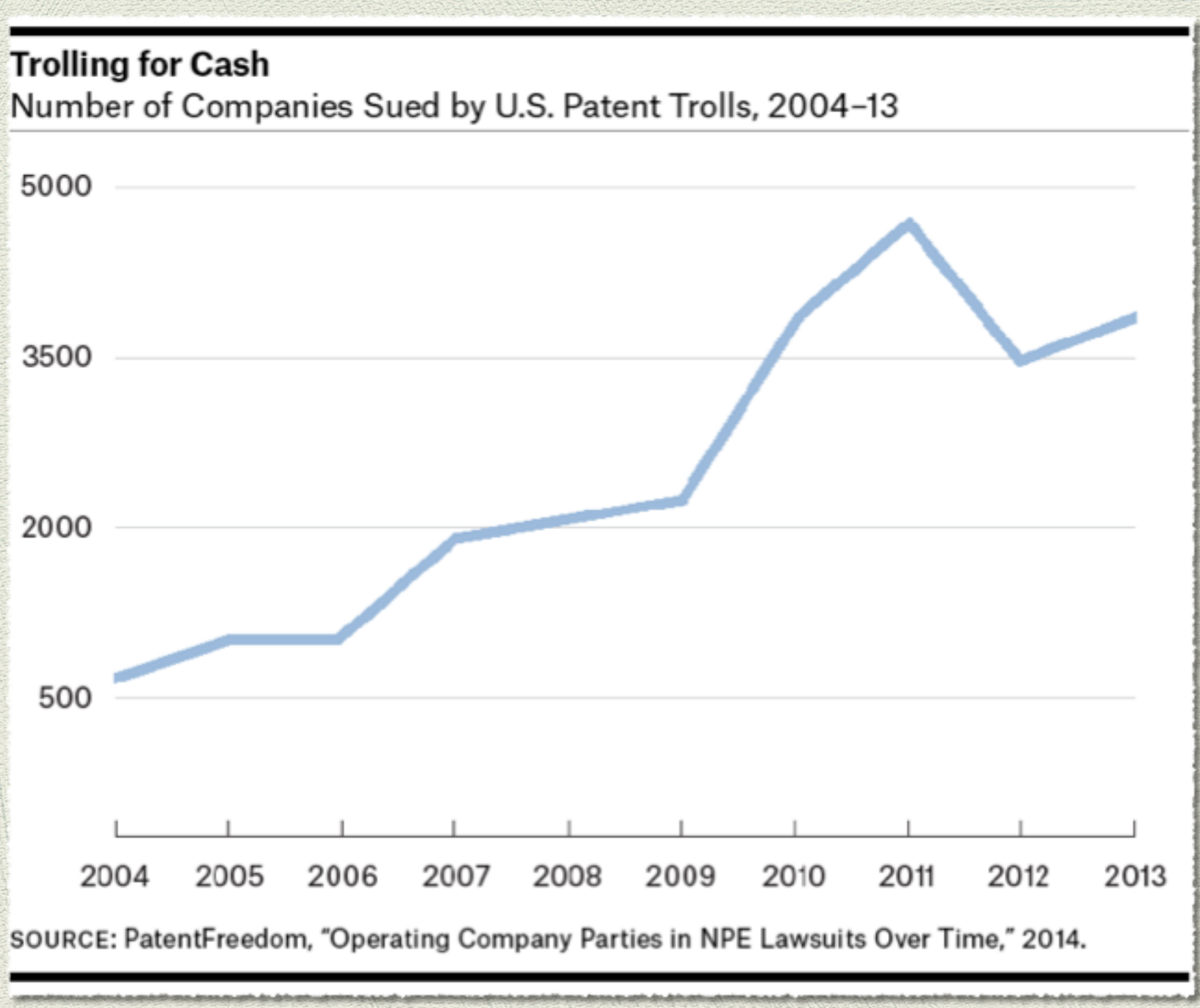
MIT's licensing income vs. research expenditure in 2011: $76M vs $1,460M - 5%!

Challenges: Start-Up Slowdown



Robert Litan. How the United States Can Regain Its Entrepreneurial Edge, Foreign Affairs, Jan/Feb, p 47-53. 2015

Challenges: The Anti-Innovators



James Bessen, How Special Interests Undermine Entrepreneurship. Foreign Affairs, Jan/Feb, p 55-60. 2015

FDA impact on US medical technology innovation.

A Survey of Over 200 Medical Technology Companies. November 2010. Josh Makower, Stanford University

- **Unpredictable, inefficient and expensive regulatory processes are jeopardizing America's leadership position in Medtech innovation.**

George Washington University Master of Engineering
Program in Regulatory Biomedical Engineering

Core Curriculum:

- BME 6482 Medical Measurements (3)
- BME 6483 Medical Instrument Design (3)
- BME 6994 Biomedical Engineering Regulatory Practicum I (3) (to be created)
- BME 6995 Biomedical Engineering Regulatory Practicum II (3) (to be created)
- MAE 3171 Patent Law for Engineers (3)
- RAFF 6201 Introduction to Global Regulatory Affairs (3)
- RAFF 6203 Regulatory Strategy in the Development of Devices and Diagnostics (3)
- RAFF 6205 Regulatory Compliance (3)

George Washington University Master of Engineering
Program in Regulatory Biomedical Engineering

Electives:

- BME 4820 Anatomy and Physiology for Engineers (3)
- BME 4830 Introduction to Medical Imaging Methods (3)
- BME 6486 Clinical Medicine for Engineers (3)
- BME 6487 Rehabilitation Medicine Engineering (3)
- CS 4531 Computer Security (3)
- CS 4532 Information Policy (3)
- ECE 6565 Telecommunication Security (3)
- EMSE 6020 Decision Making with Uncertainty (3)
- EMSE 6765 Data Analysis for Engineers and Scientists (3)
- MAE 6204 Tissue Engineering (3)
- MAE 6238 Biomaterials (3)

Outline

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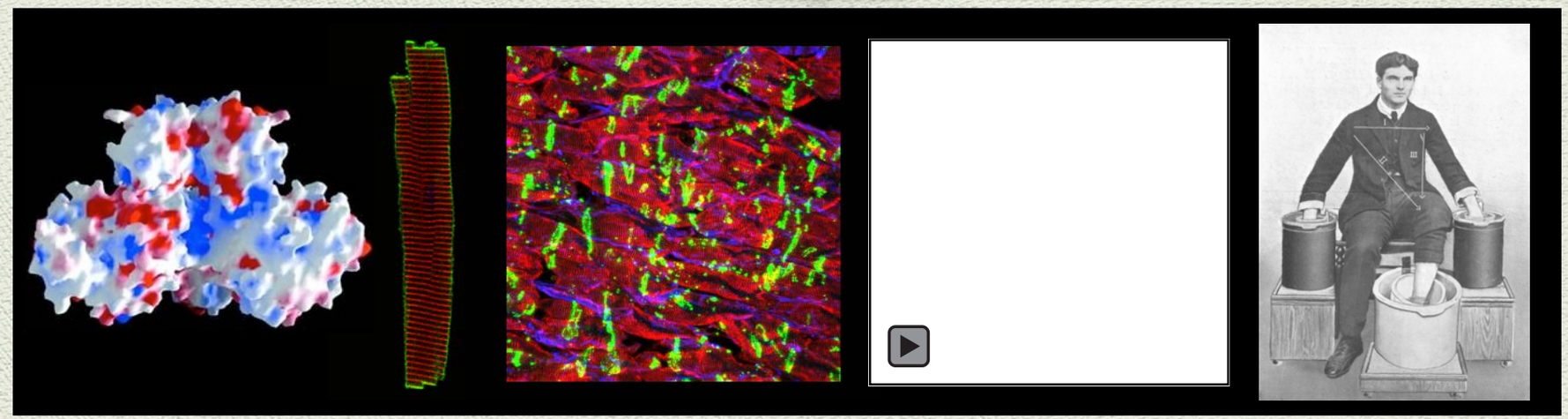
- Patient-specific therapies

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

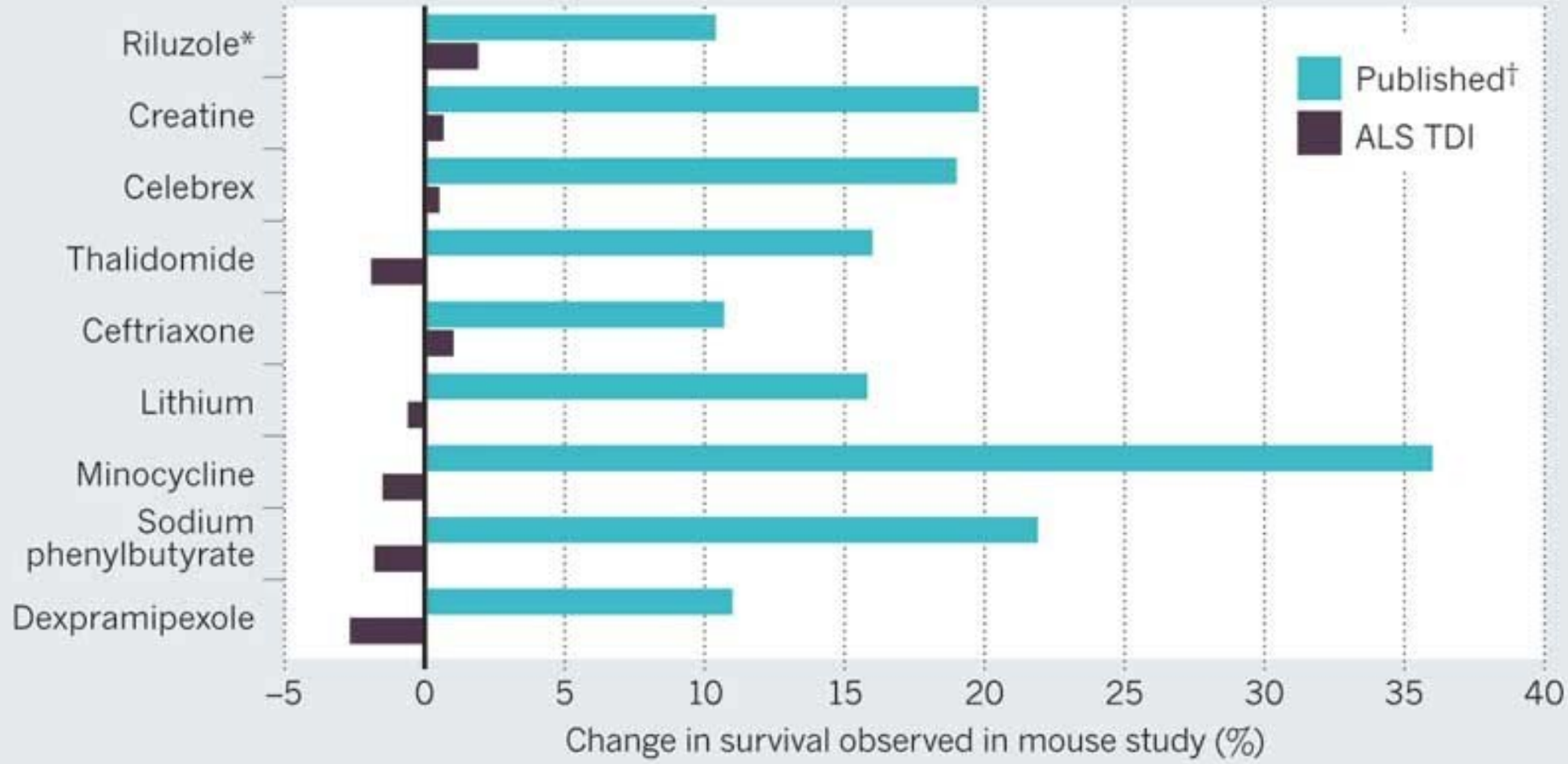
Jessica Bolker. Model organisms: There's more to life than rats and flies. Nature 491, 31–33, 2012

- "... 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"

Due Diligence, Overdue

DUE DILIGENCE, OVERDUE

Results of rigorous animal tests by the Amyotrophic Lateral Sclerosis Therapy Development Institute (ALS TDI) are less promising than those published. All these compounds have disappointed in human testing.



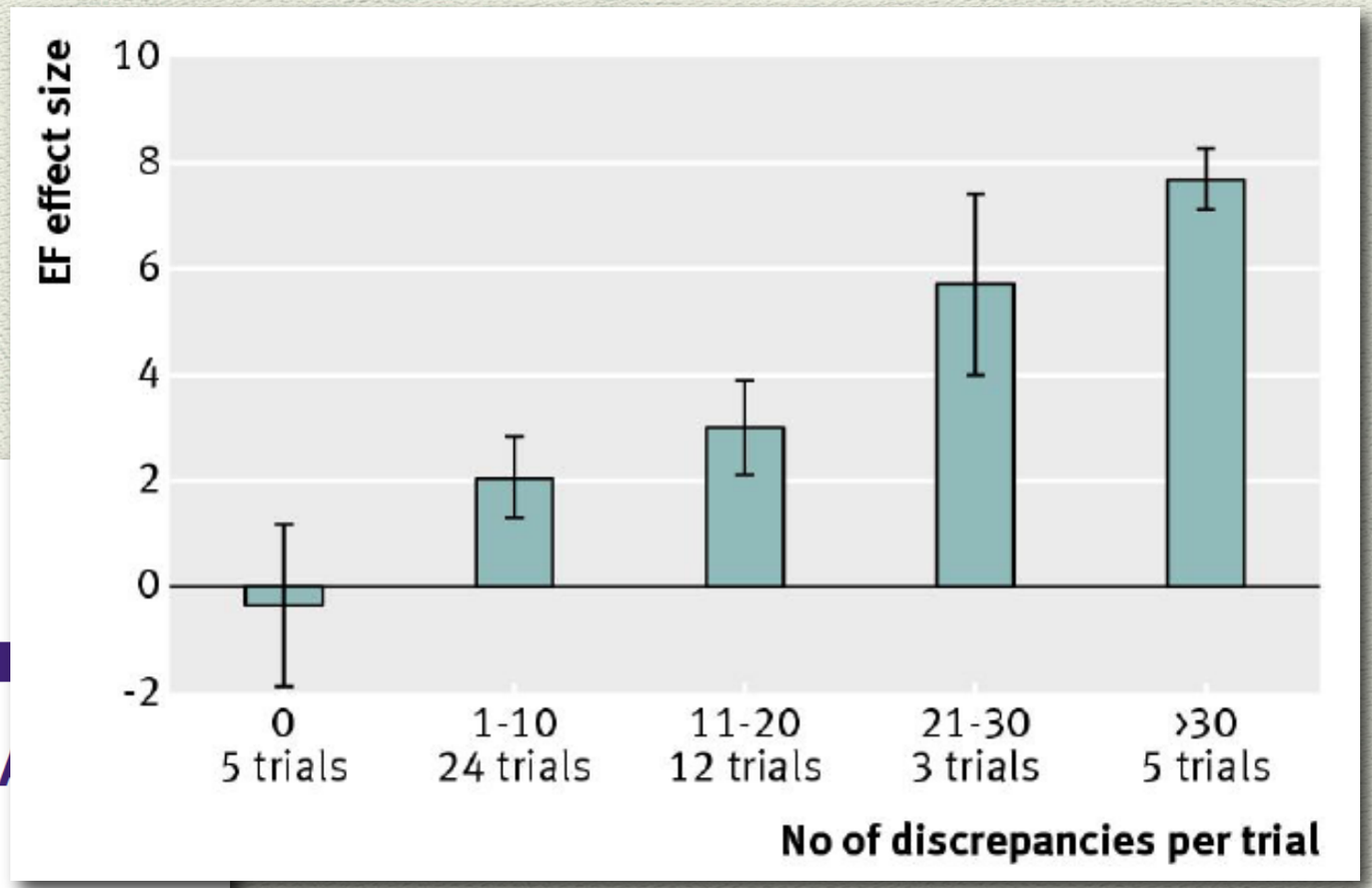
*Although riluzole is the only drug currently approved by the US Food and Drug Administration for ALS, our work showed no survival benefit.
†References for published studies can be found in supplementary information at go.nature.com/hf4jf6.

Perrin: Nature, 507: 423-425, 2014

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.”

Mean ejection fraction (EF) effect size by number of discrepancies in trial's reports



BMJ

BMJ 2014;348:g2688 doi: 10.1136/bmj.g2688 (Published 29 April 2014)

RESE

Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis

Alexandra N Nowbar *cardiovascular scientist*, Michael Mielewczik *postdoctoral biologist*, Maria Karavassilis *clinical medical student*, Hakim-Moulay Dehbi *statistician*, Matthew J Shun-Shin *academic clinical fellow in cardiology*, Siana Jones *cardiovascular physiologist*, James P Howard *physician*, Graham D Cole *BHF clinical research training fellow*, Darrel P Francis *professor of cardiology*, on behalf of the DAMASCENE writing group

International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London W2 1LA, UK

Opportunities for Human Heart Research: OPOs

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

K. K. Khush[1,*], J. G. Zaroff[2], J. Nguyen[3], R. Menza[4] and B. A. Goldstein[5]

[1]*Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA*
[2]*Kaiser Northern California Division of Research, Oakland, CA*
[3]*California Transplant Donor Network, Oakland, CA*
[4]*Graduate School of Nursing, Midwifery, and Health, Victoria University of Wellington, Wellington, New Zealand*
[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 assist fraction; MPSC, Committee; OE, Procurement an 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

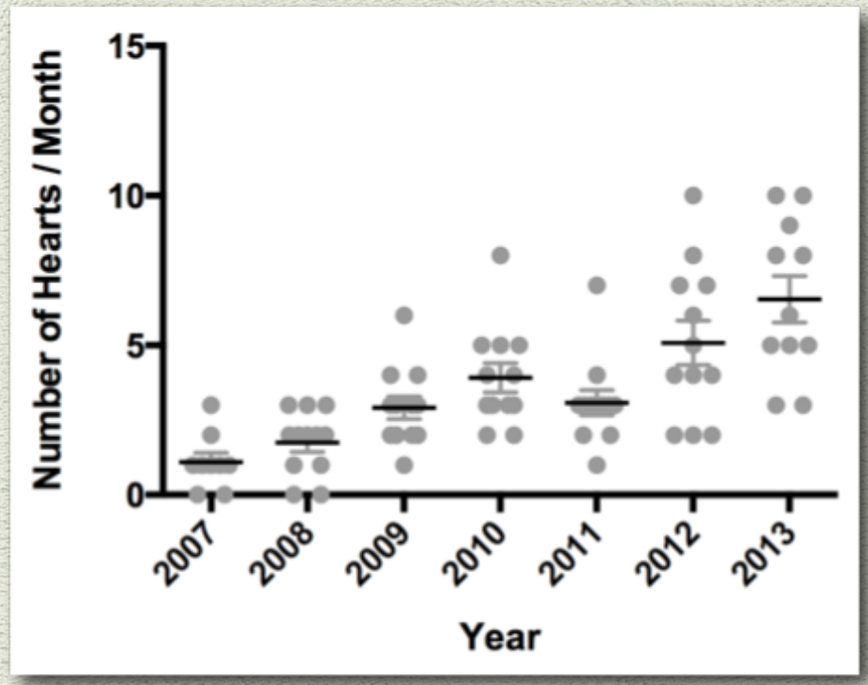
M. B. M. Doyle[1,*], N. Vachharajani[1], J. R. Wellen[1], J. A. Lowell[1], S. Shenoy[1], G. Ridolfi[1], M. D. Jendrisak[2], J. Coleman[3], M. Maher[3], D. Brockmeier[3], D. Kappel[3] and W. C. Chapman[1]

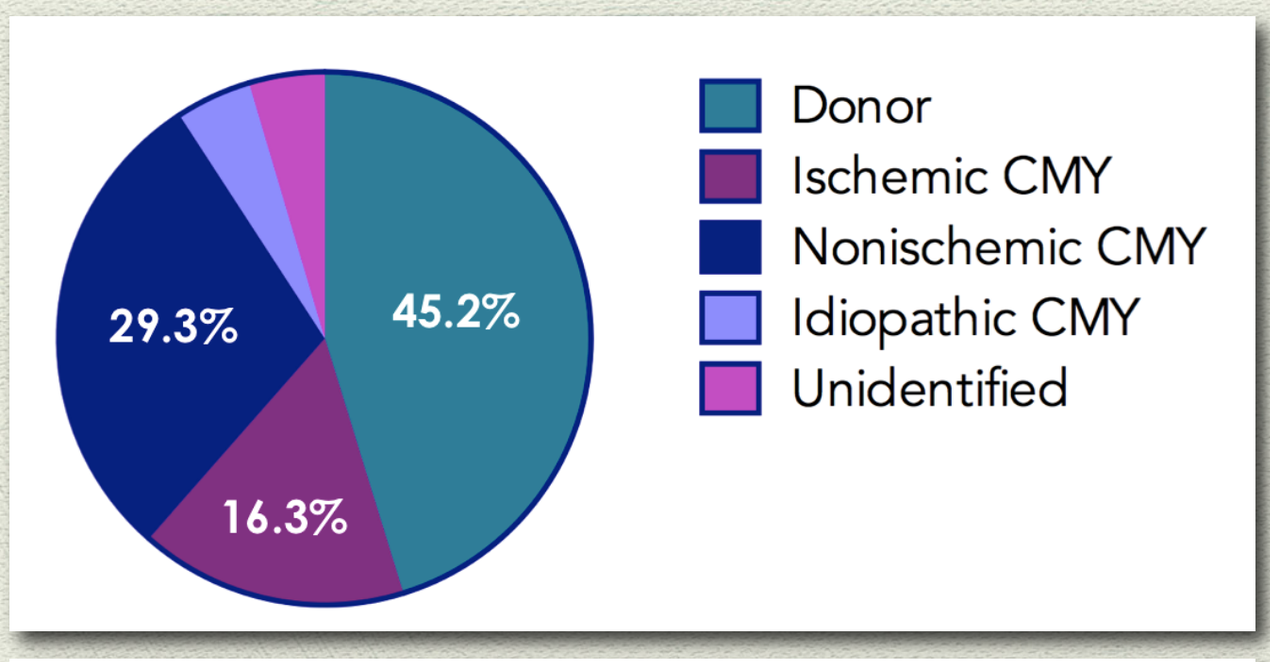
[1]*Department of Surgery, Washington University School of Medicine, St. Louis, MO*
[2]*Gift of Hope, Chicago, IL*
[3]*Mid America Transplant Services, St. Louis, MO*
[*]*Corresponding author: M. B. Majella Doyle, doylem@wustl.edu*

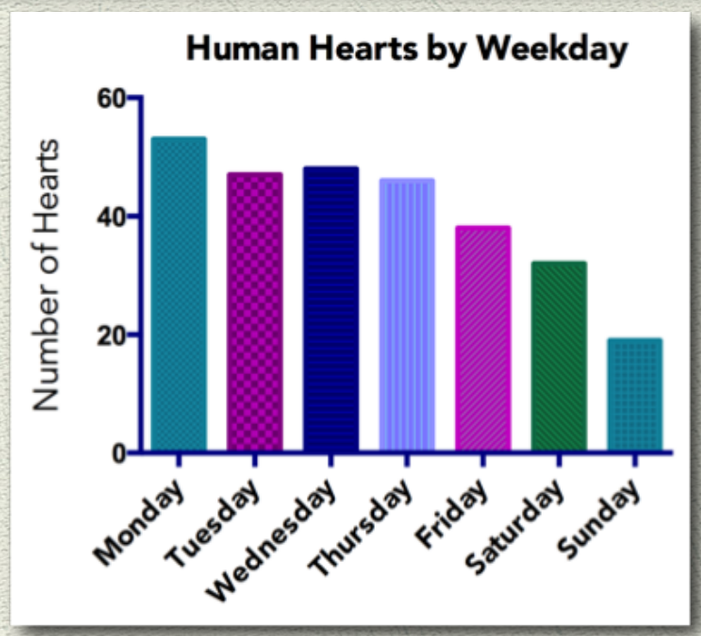
Introduction

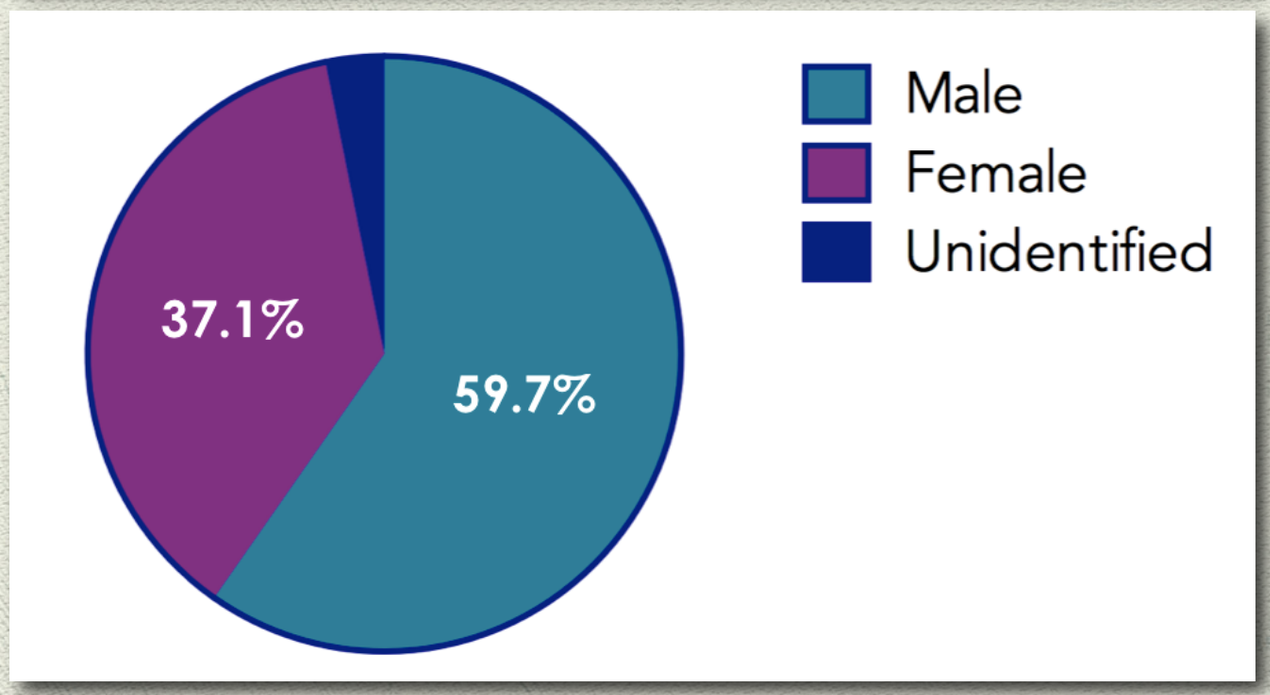
In the United States, the experience of donor procurement is often time consuming and logistically challenging for organ procurement organizations (OPOs) and organ recipient centers. Typically, transplant surgeons from the recipient center travel to the organ donor's hospital and perform complex, time-sensitive 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
(352 human hearts)









Outline

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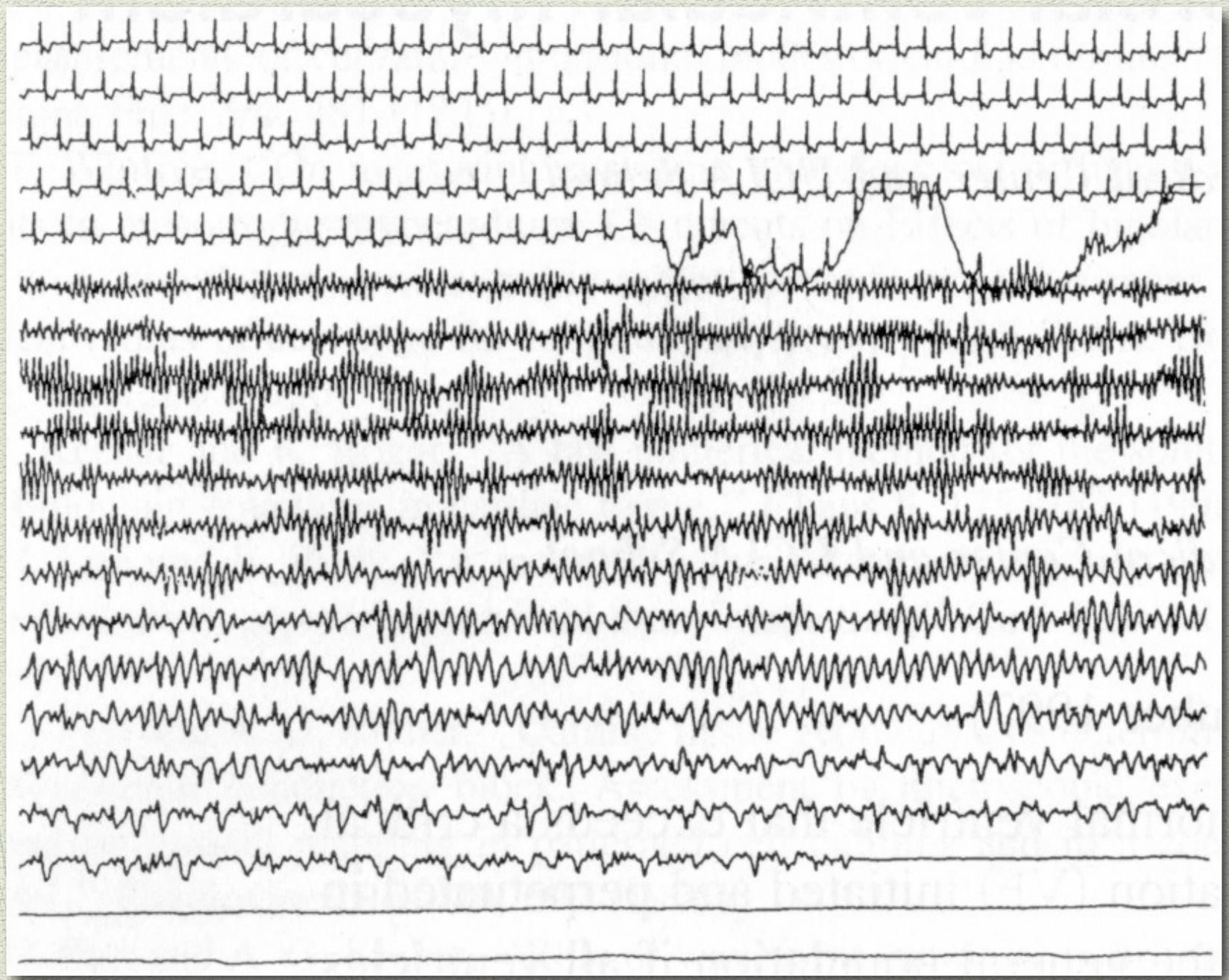
- Patient-specific therapies

Documented sudden cardiac death



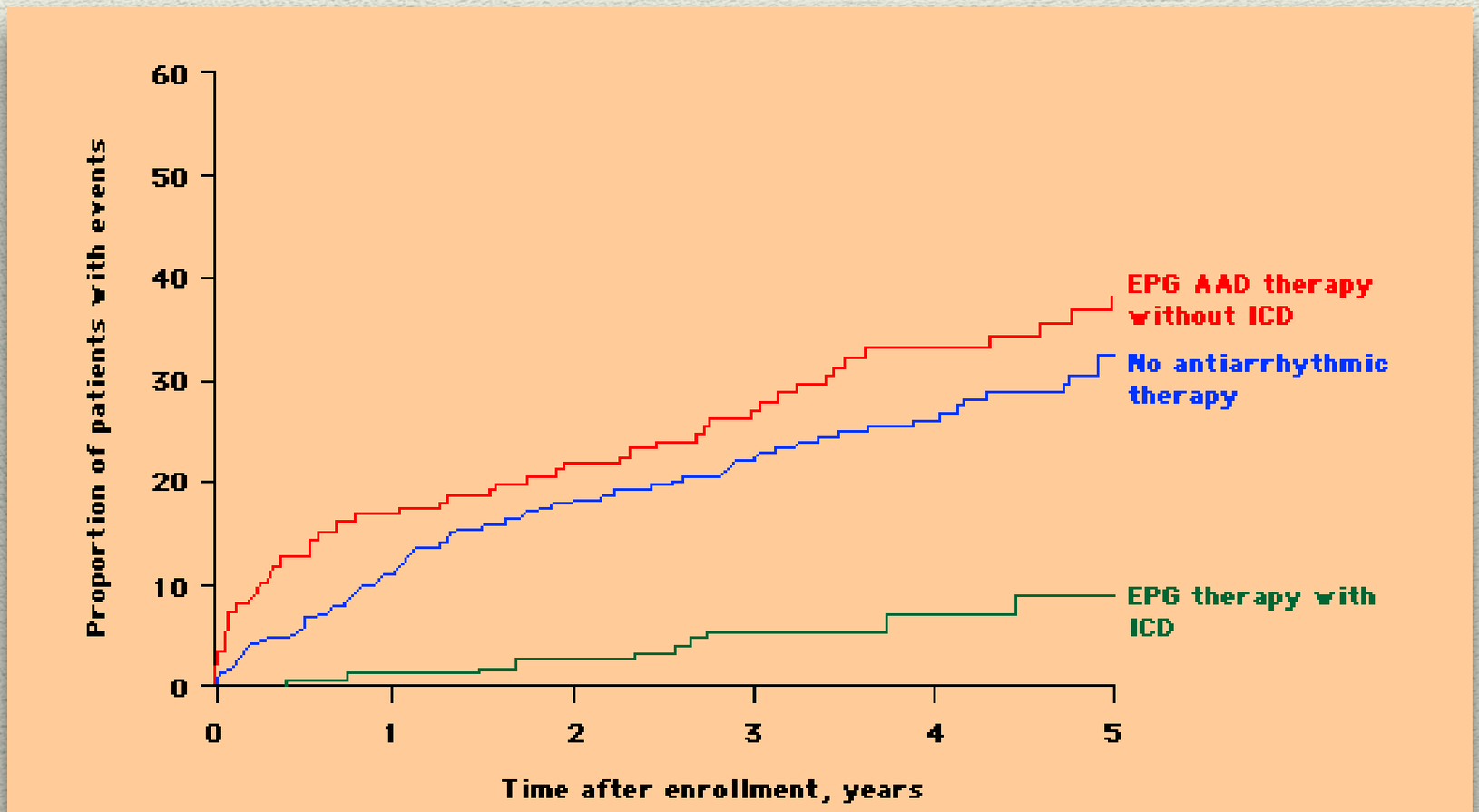
Spontaneous VF and sudden cardiac death. This figure shows a portion of a 24-h ECG recording from a patient who died a sudden cardiac death. The lines are separated by 1 minute.

P.-S.Chen et al, Computerized mapping of fibrillation in normal ventricular myocardium,Chaos, 8: 127-136, 1998

Early history of resuscitation

An XVIII-century attempt at resuscitating a human patient by blowing smoke into the rectum and applying electric stimulation to the chest cavity. Courtesy of Wood Library-Museum of Anesthesiology, Park Ridge, Illinois.

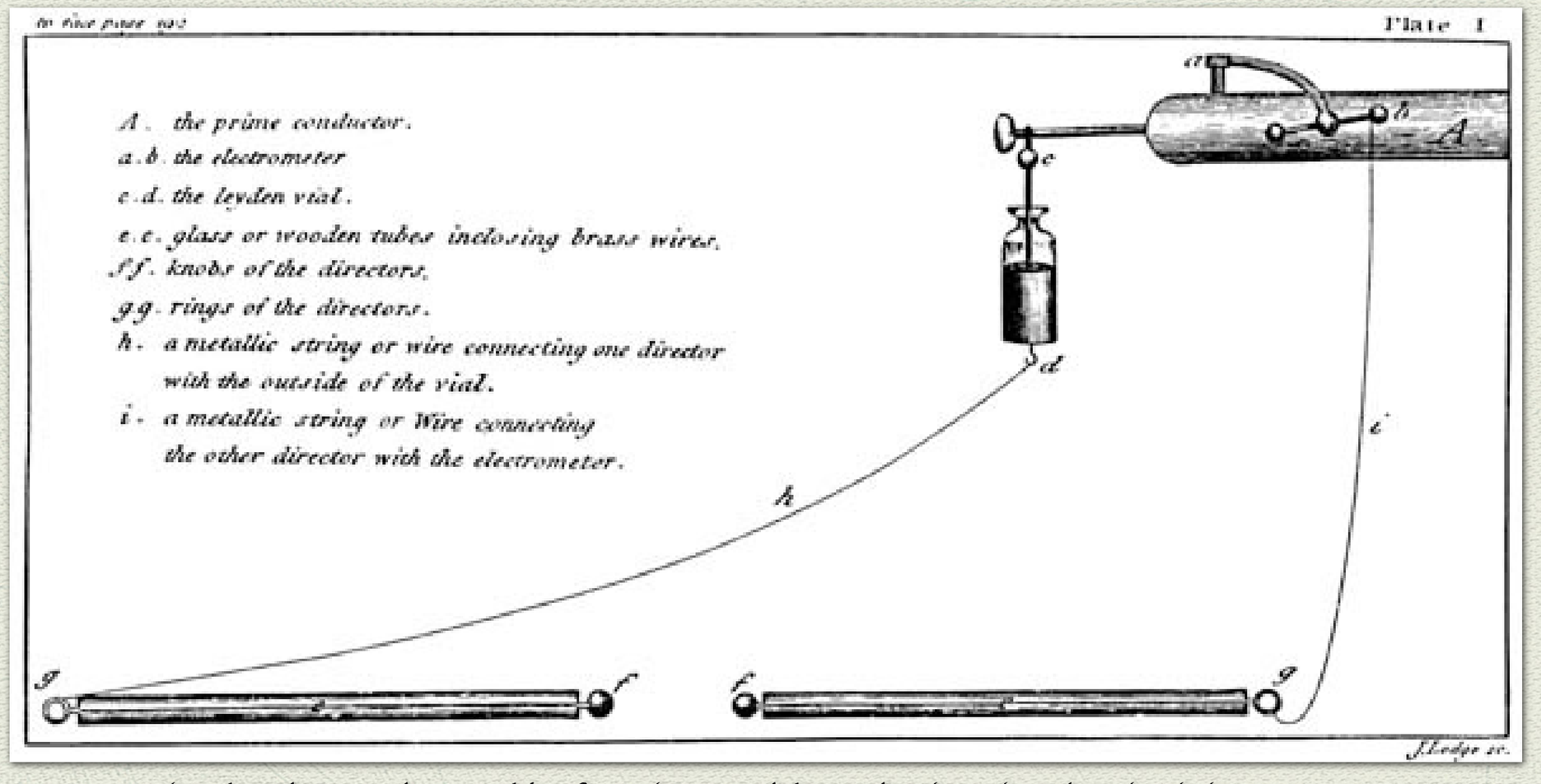
Failure of Antiarrhythmic Drug Therapy



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).

Charles Kite,

An Essay on the Recovery of the Apparently Dead, London, 1788.



"...Twenty minutes had at least elapsed before he could apply the shock, which he gave to various parts of the body without any apparent success; but at length, on transmitting a few shocks through the thorax, he perceived a small pulsation; soon after the child began to breathe, though with great difficulty. In about ten minutes she vomited. A kind of stupor remained for some days; but the child was restored to perfect health and spirits in about a week".

1792 report in the Gentlemen's Magazine on Fell's Electrical Machine

colour. This effect is likewise, I apprehend, produced on the immature unexcluded *ova* within the body of the lobster, which are generally found of a beautiful red colour after having been exposed to the heat of boiling water.

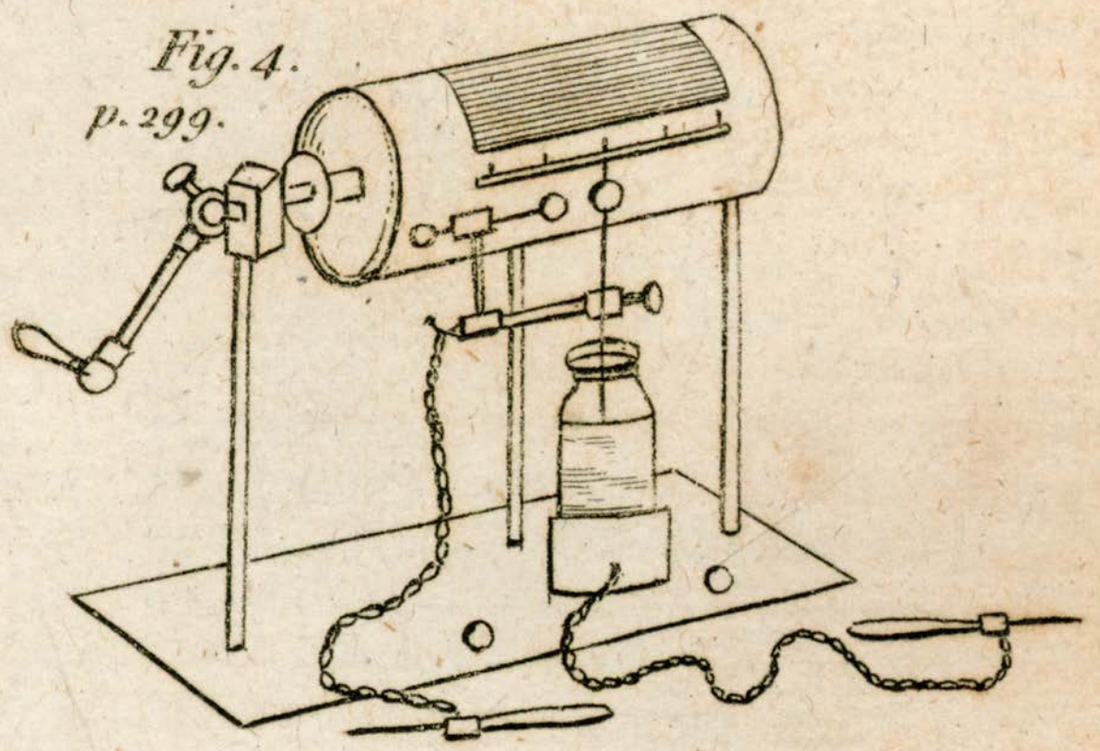
Yours, &c. H.

Mr. URBAN, *Ulverstone, April 2.*

ON looking over the Reports of the Lancashire Humane Society, I met with a description and print of a portable electrical machine, by Mr. Fell, surgeon, Ulverstone; which, from its simplicity, small size, &c. seems so well calculated for its intended purpose of restoring suspended respiration, that it ought to be universally known. To answer this end, no mode appeared so likely as procuring it a place in the Gentleman's Magazine; I shall, there-

pillars are to be covered with good sealing-wax, which is to be rubbed on the surface of the heated glass; or with amber-varnish, or with linseed oil, baking the glass in an

Fig. 4.
p. 299.



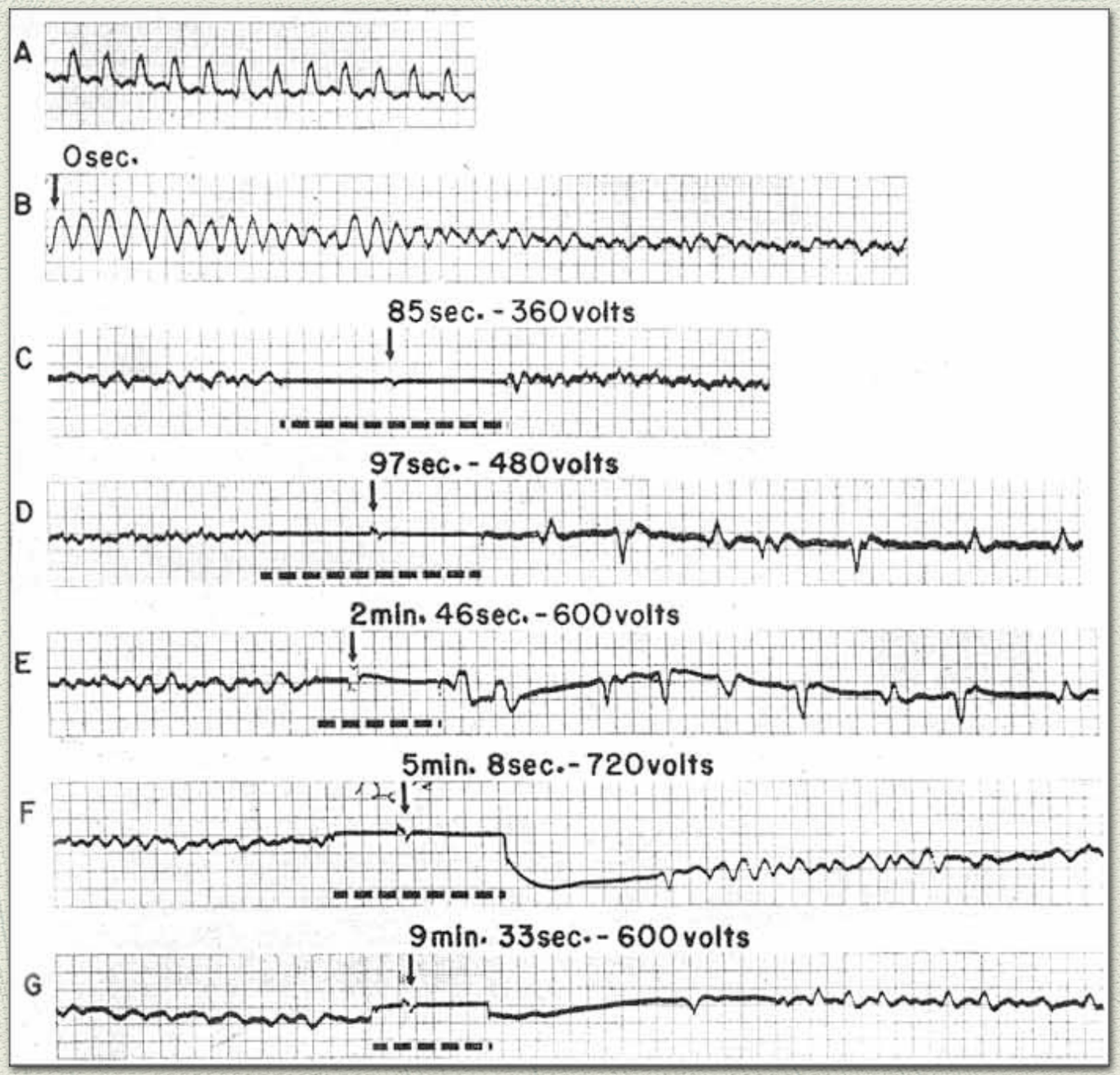
C.S. Beck, W.H. Pritchard, H.S. Feil,

Ventricular fibrillation of long duration abolished by electric shock.
JAMA. 135: 985, 1947

AC defibrillation

Zoll PM, Linenthal AJ, Gibson W, Paul M, Norman LR.

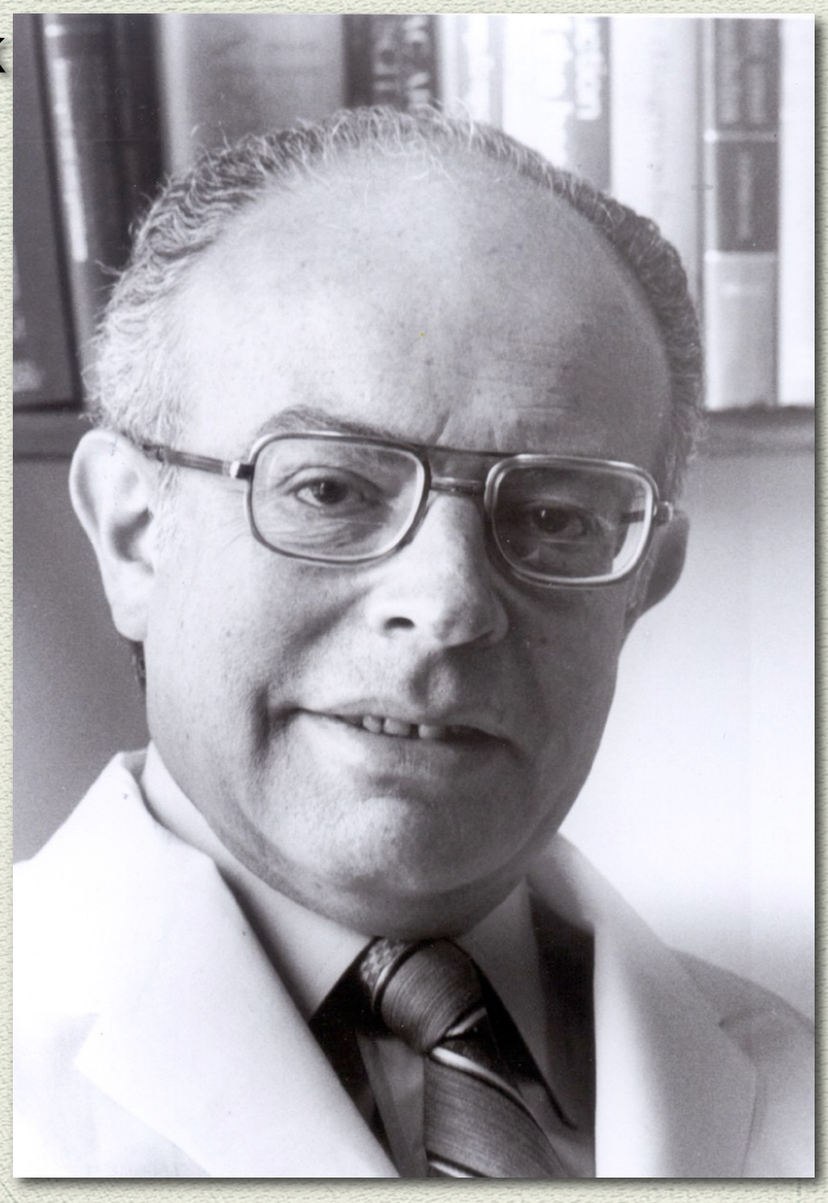
Termination of Ventricular Fibrillation in Man by Externally Applied Electrical Countershock. New Eng J Med 1956; 254: 727-732.



Paul M. Zoll (1911-1999)

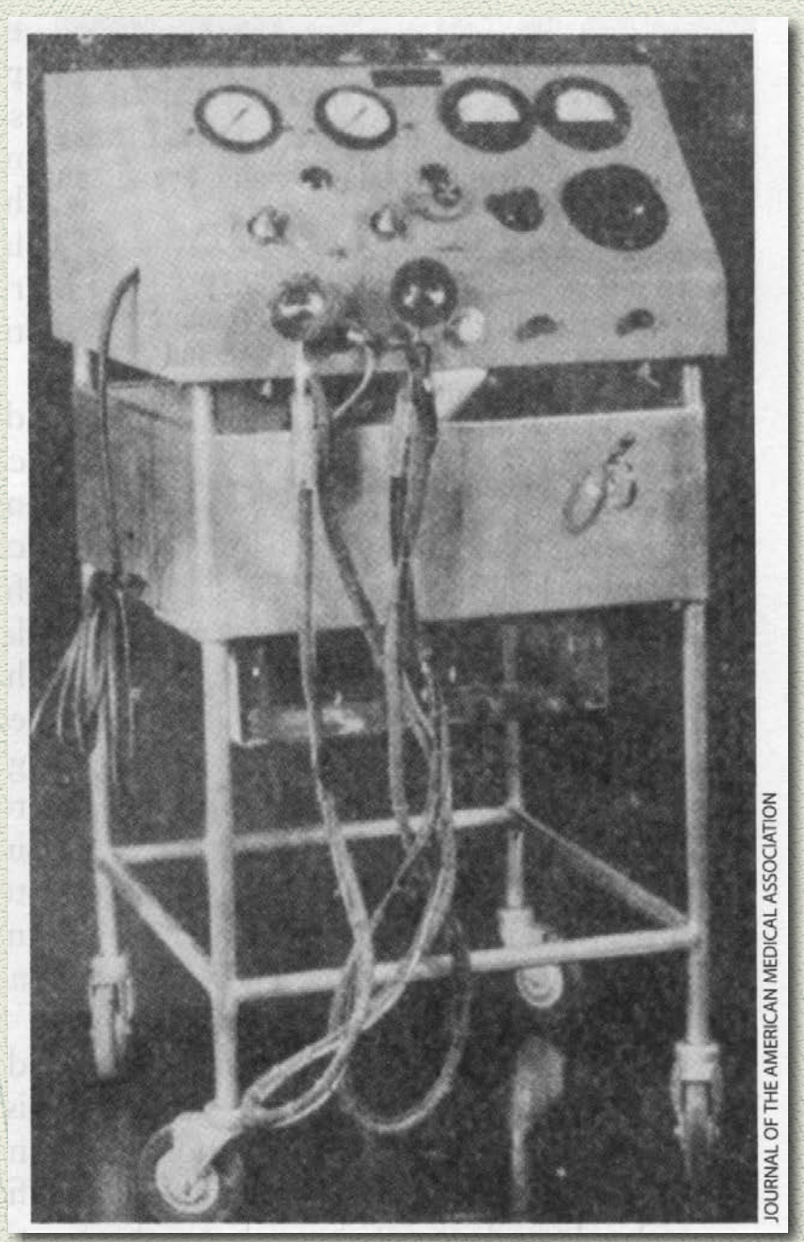
Automatic Implantable Defibrillator

- Mirowski M, Mower MM, Staewen WS, Tabatznik B, Mendeloff AL. Standby automatic defibrillator: An approach to prevention of sudden coronary death. Arch Intern Med. 1970; 126:158-161.
- Schuder JC, Stoeckle H, Golg JH, et al. Experimental ventricular defibrillation with an automatic and completely implanted system. Trans Am soc Artif Organs. 1970; 16:207-212.
- Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med. 1980; 303:322-4.



Michel Mirowski, 1924-1990

Implantable technology development



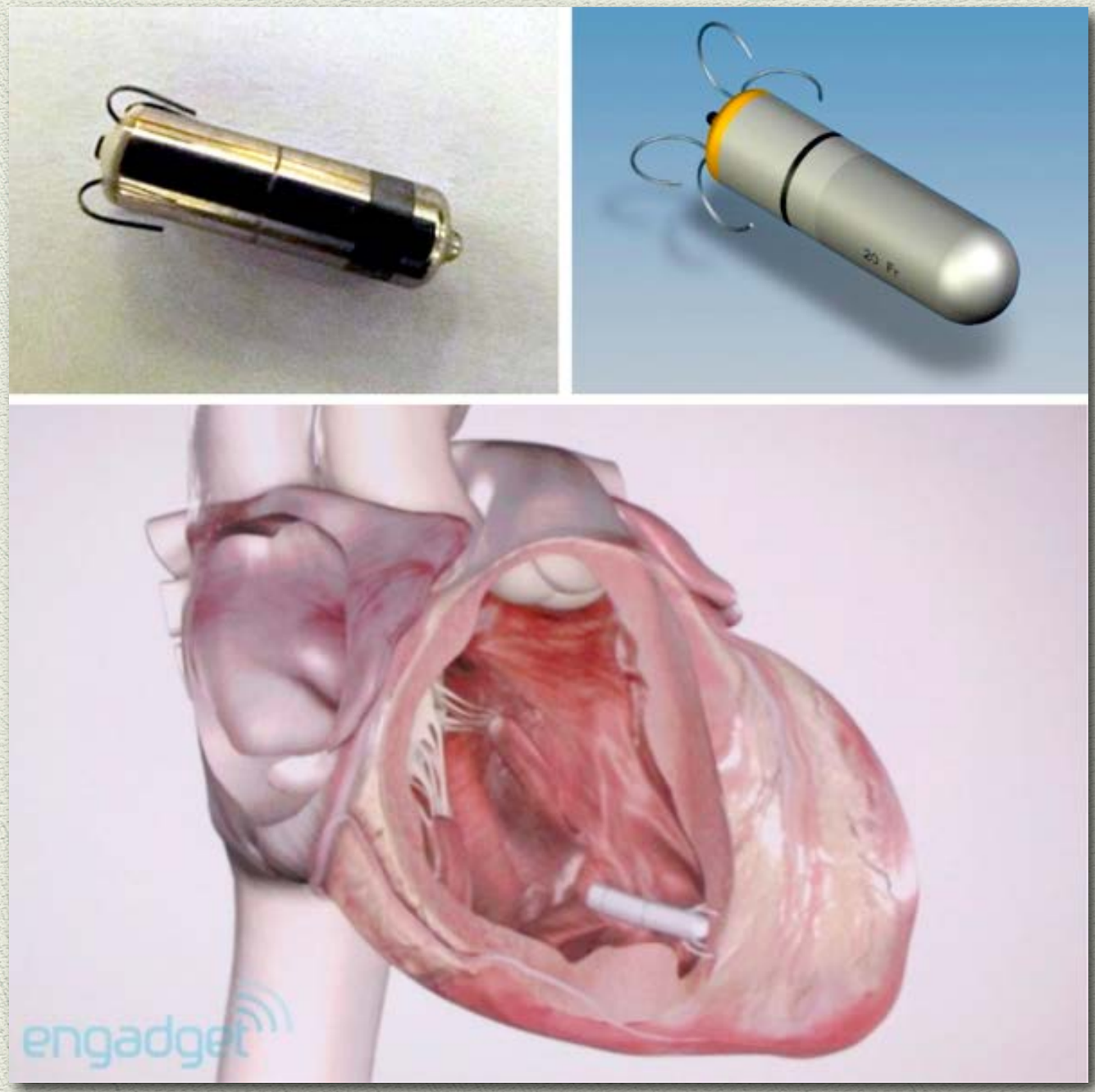
Dr. Beck's defibrillator 1947

Automatic Implantable Cardioverter Defibrillator (ICD)

Bradycardia and Resynchronization

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

Leadless pacemakers



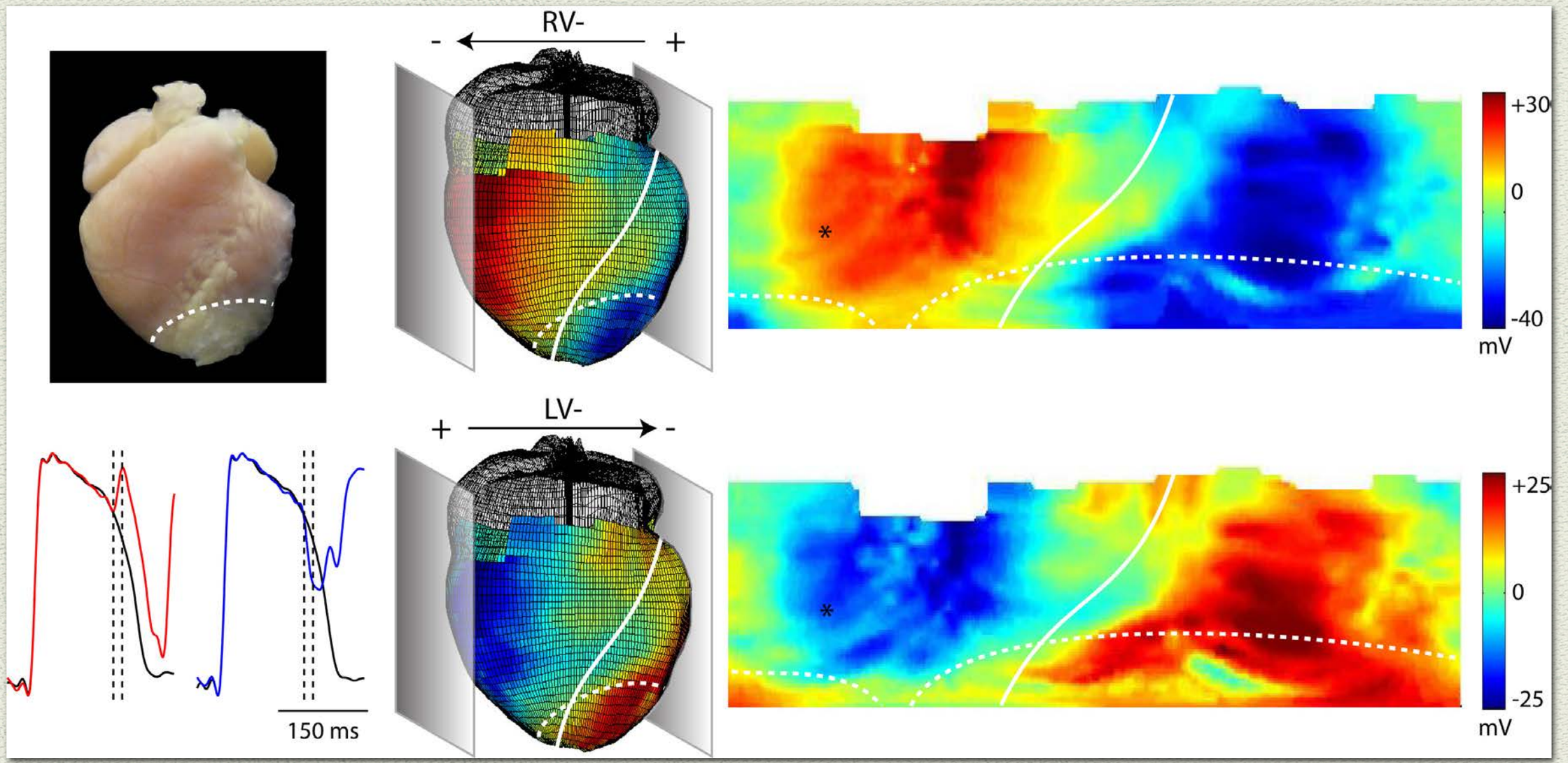
Ventricular Fibrillation: 400,000 Sudden Deaths per Year (US)

- 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)

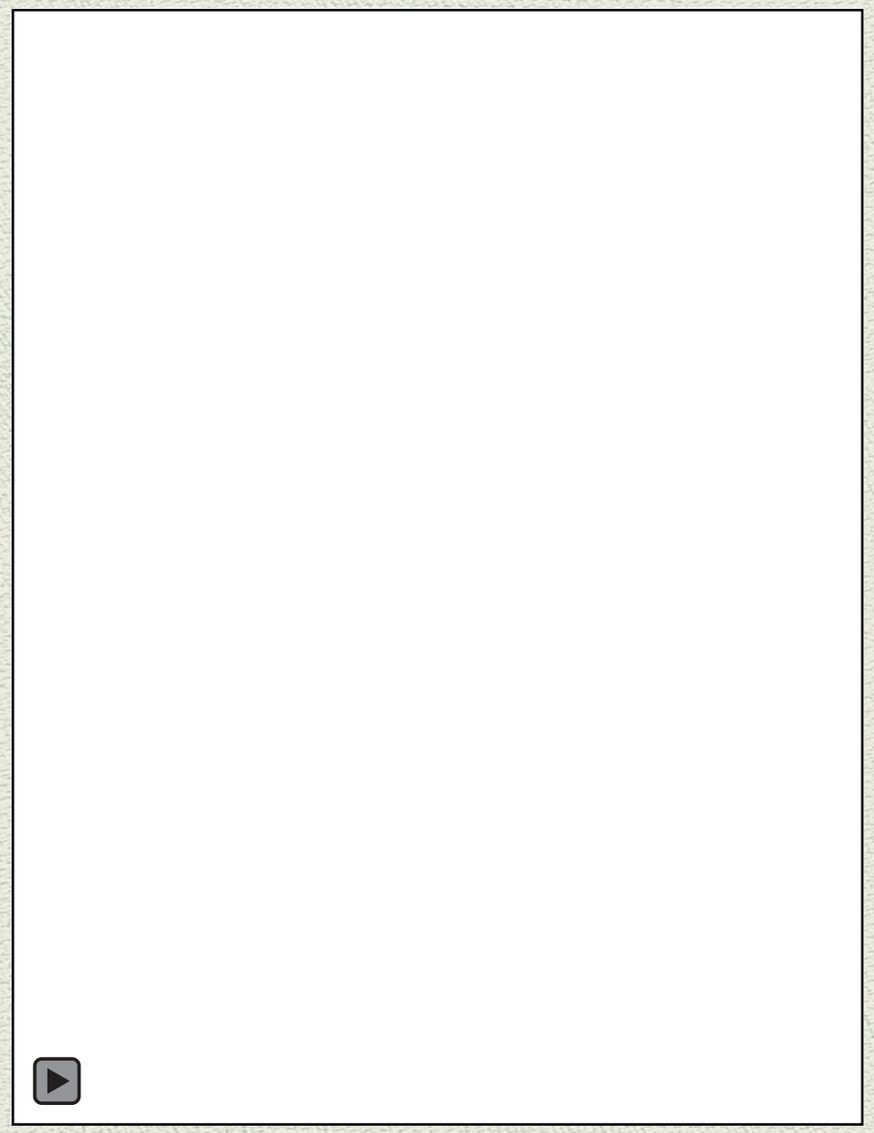
- Antiarrhythmic drug therapy: efficacy 15% and side effects
- Ablation: high recurrence, less effective in persistent
- Implantable device therapy: none, too painful

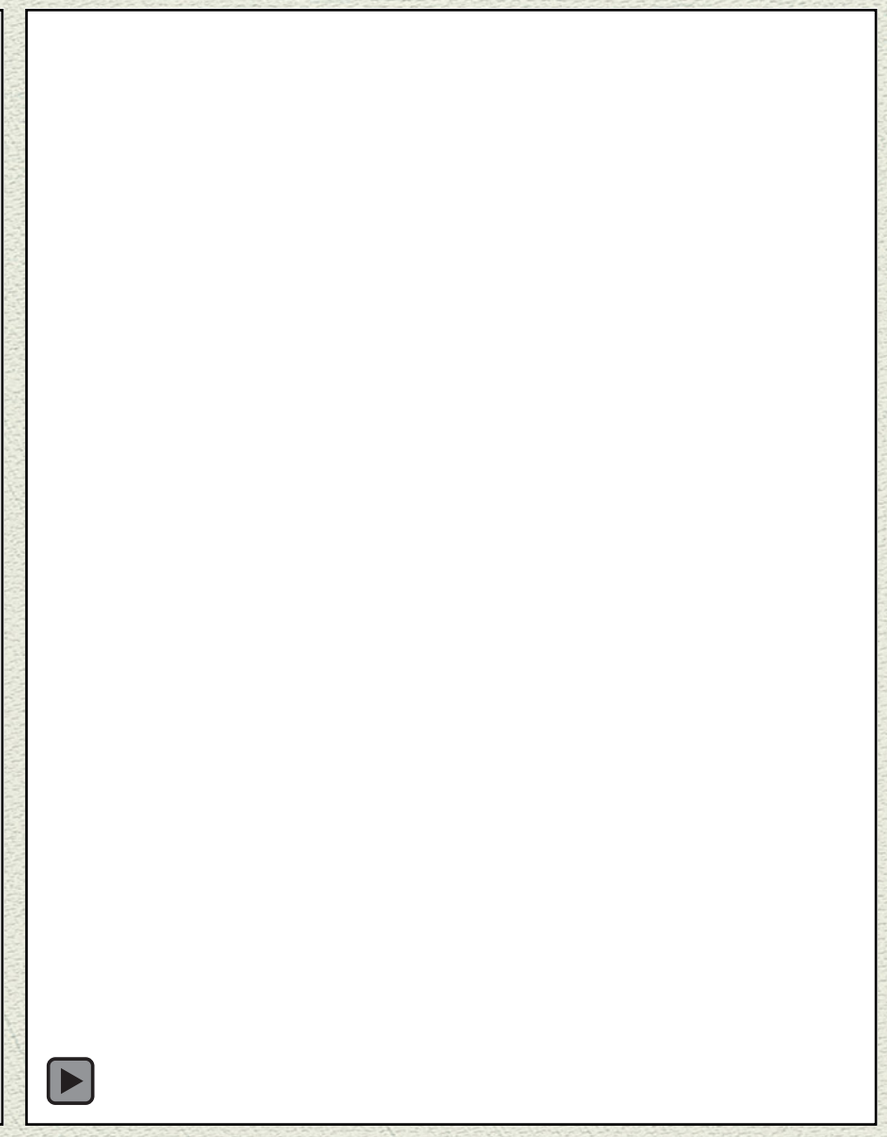
Optical mapping of virtual electrode polarization in rabbit model of external defibrillation



Ripplinger et al, 2008

Optimization of defibrillation: Monophasic vs. Biphasic Shock



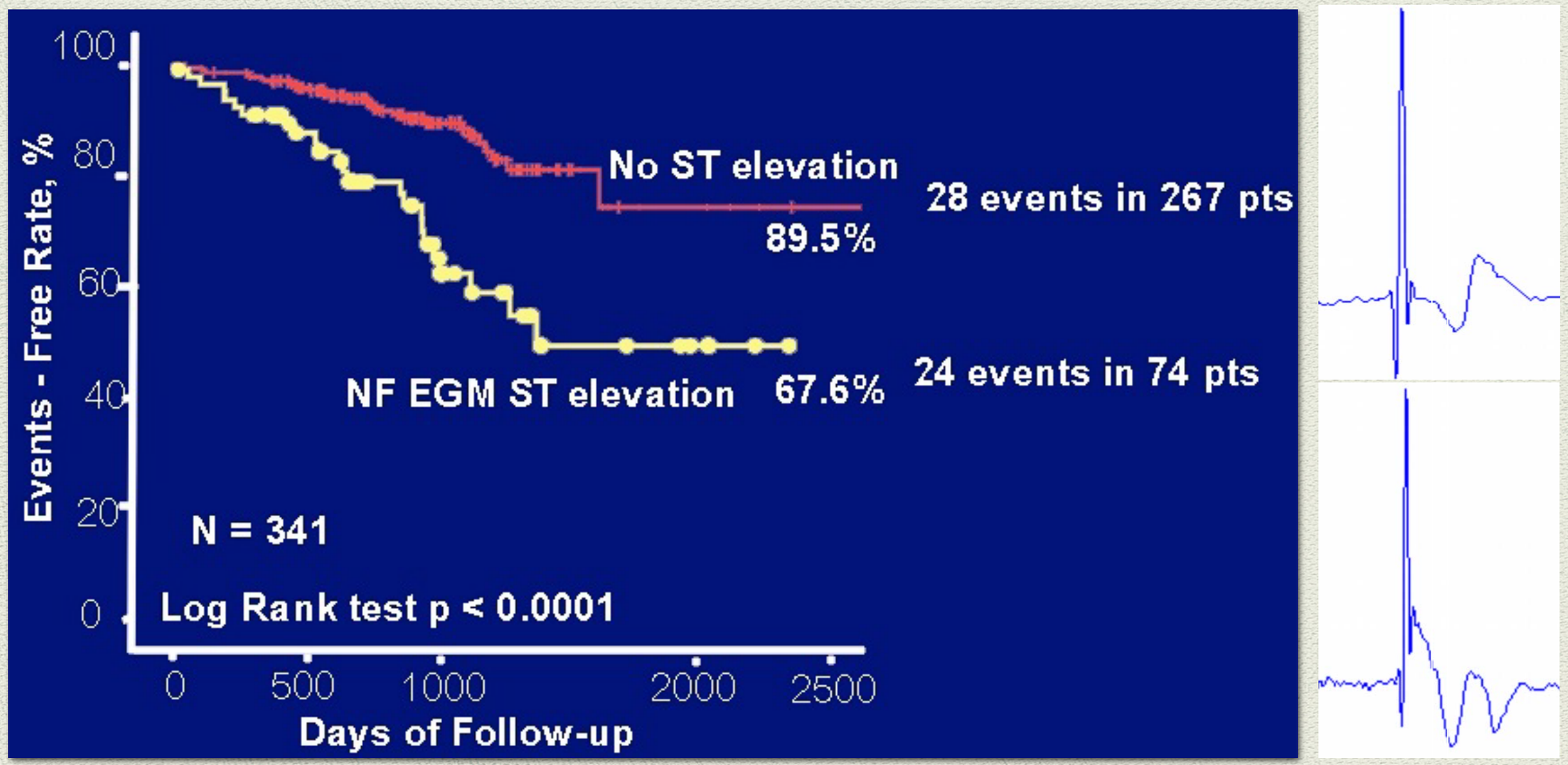


Monophasic shock

Biphasic shock

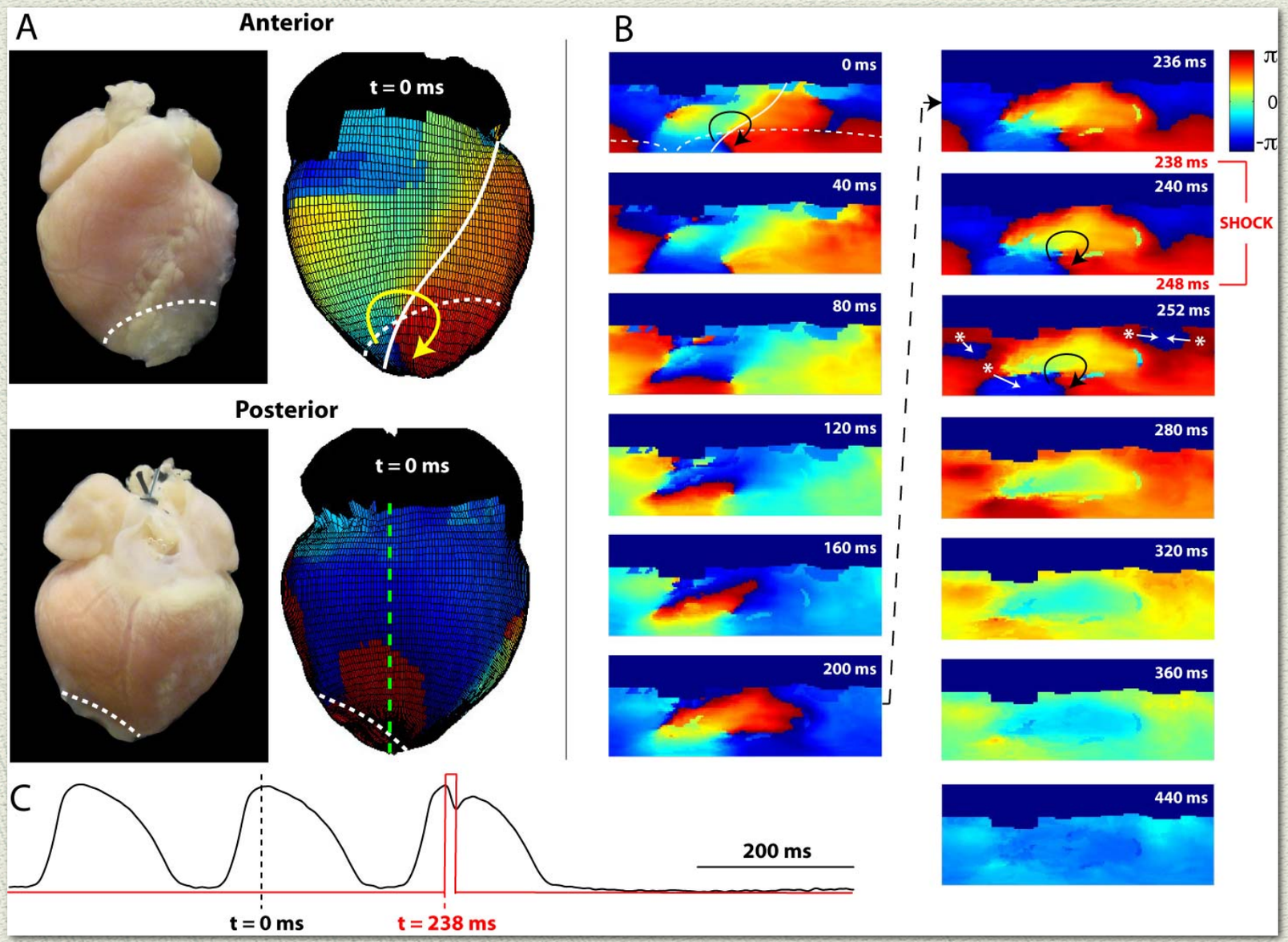
Efimov et al, 1998

Increased Heart Failure Risk with ST Elevation / Local Injury Current



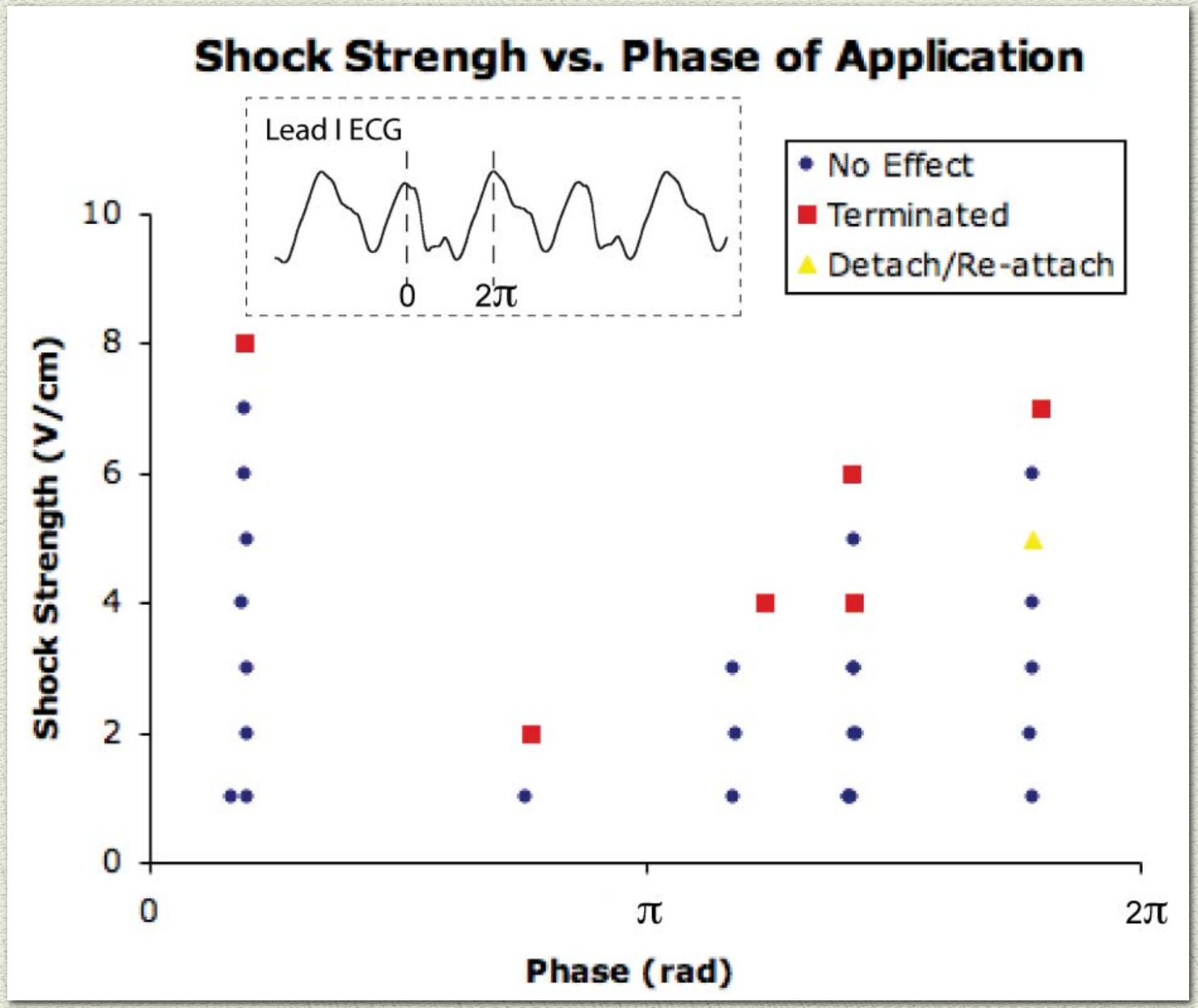
Tereshchenko et al, JACC, 2009

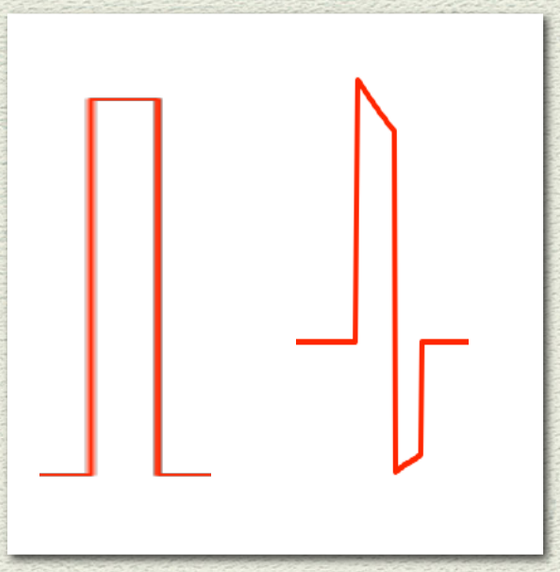
Termination of VT by a single properly-timed low energy shock



Ripplinger, 2009

Phase-dependency of a Single Shock Cardioversion



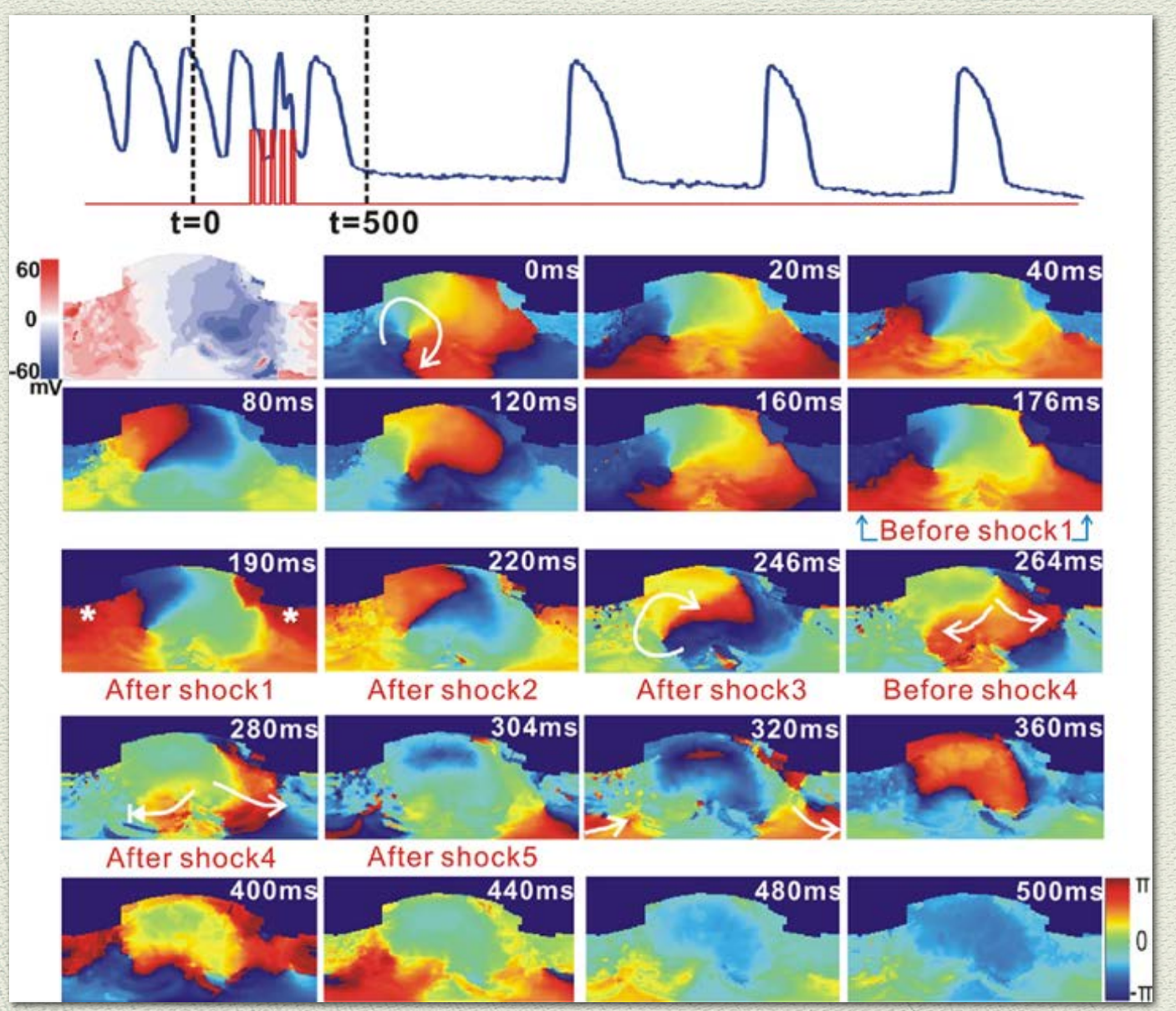


1MP Max vs Min:
7.8 ± 1.9 vs. 4.1 ± 1.6 V/cm

1BP Max vs Min:
8.6 ± 1.7 vs. 3.7 ± 1.9 V/cm

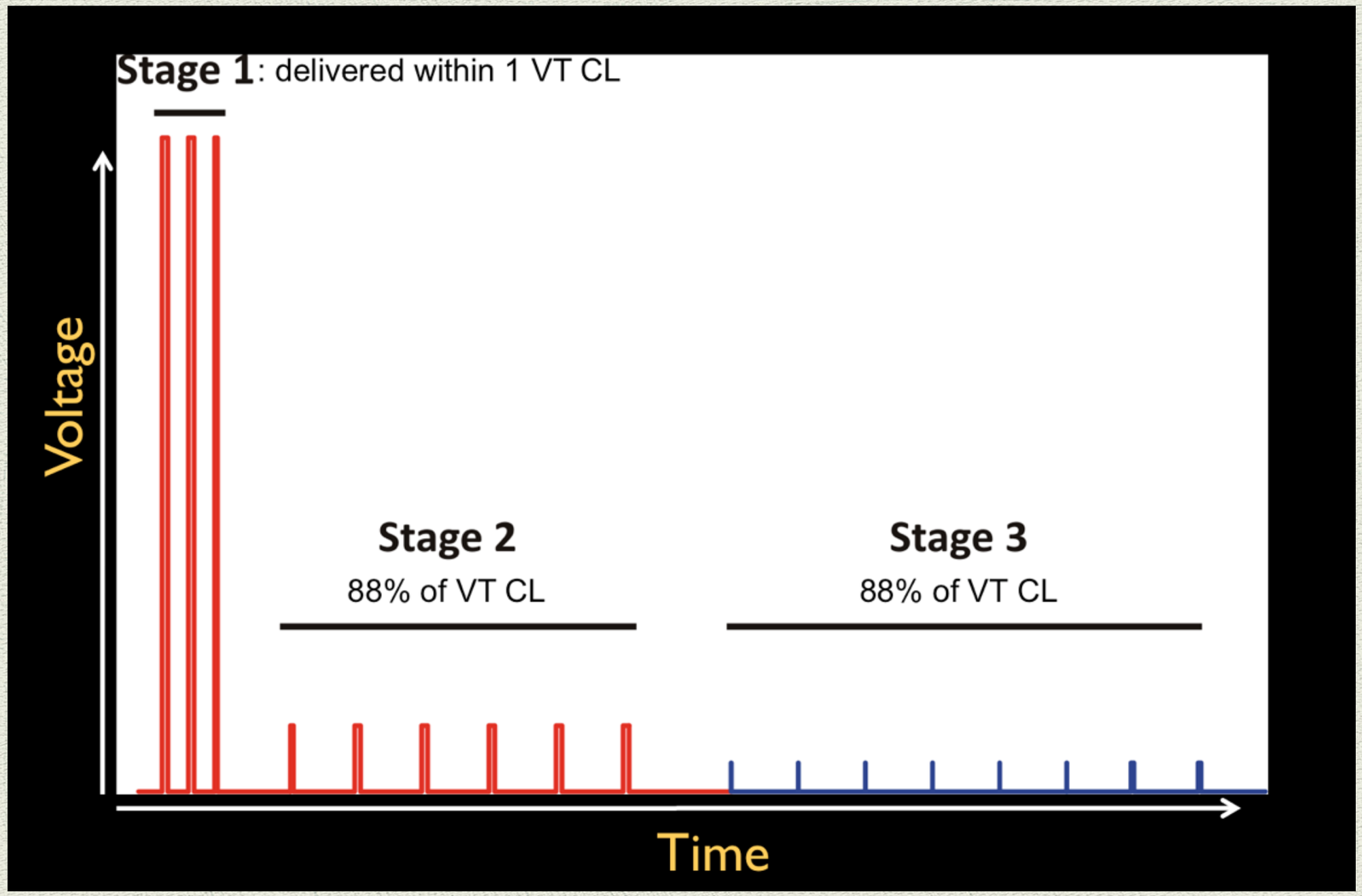
Ripplinger, 2009; Li, 2009

Multiple Shocks Terminate VT With Lower Field Strength Than a Single Shock In an ex vivo Rabbit Model



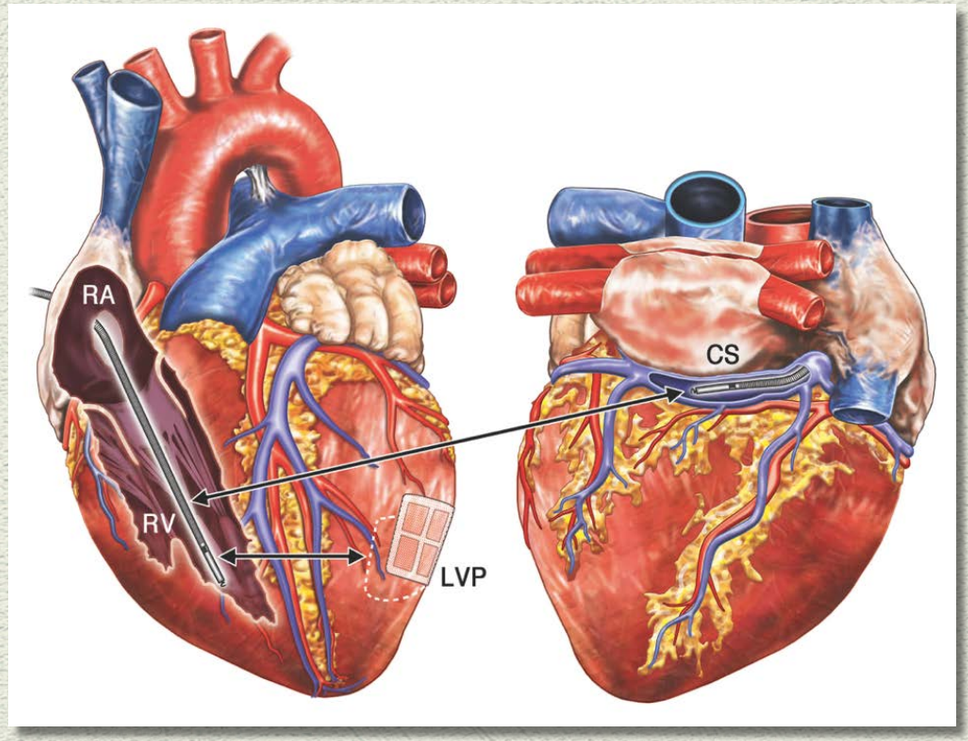
Li W, Ripplinger CM, Lou Q, Efimov IR. **Multiple monophasic shocks improve electrotherapy of ventricular tachycardia in a rabbit model of chronic infarction.** Heart Rhythm **(**2009) 6:1020-1027.

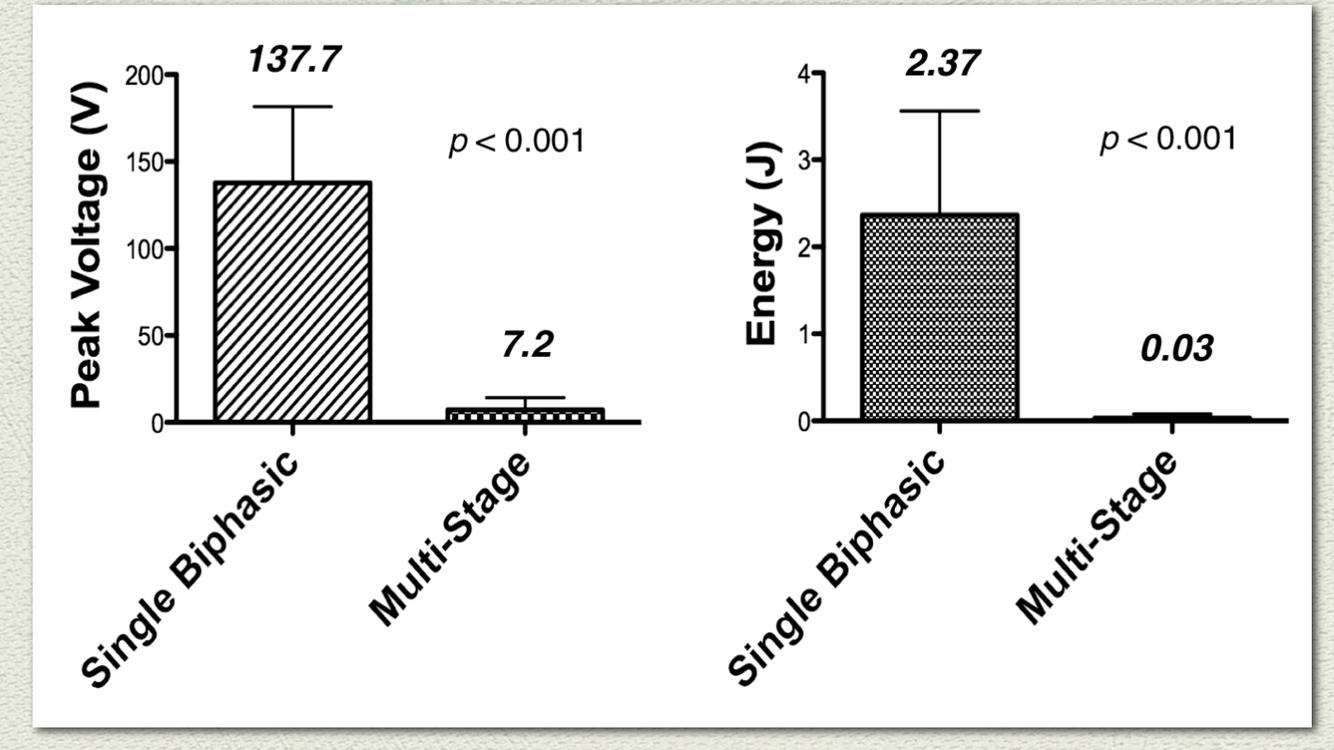
Multiple-stage Electrotherapy

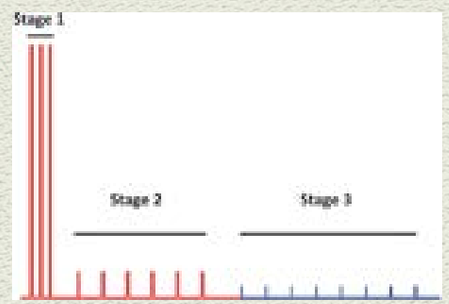


Janardhan et al, JACC, 2012

Low energy ventricular defibrillation





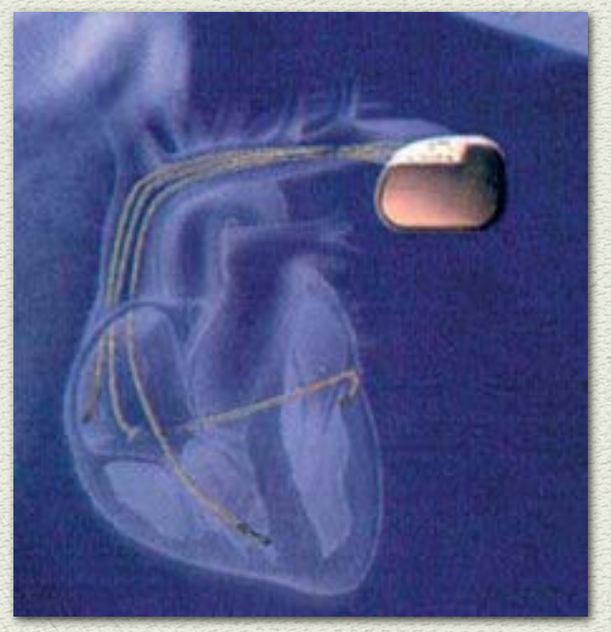


- Peak shock voltage was 7.2 ± 6.9 V versus 137.7 ± 43.8 V for a single BP shock.
- Mean DFT was 0.03 ± 0.05 J versus 2.37 ± 1.20 J for a single BP shock.

AF cardioversion

- Cardioversion of Atrial Fibrillation (AF) to sinus rhythm using a single high-energy external shock remains a mainstay of therapy for symptomatic patients.

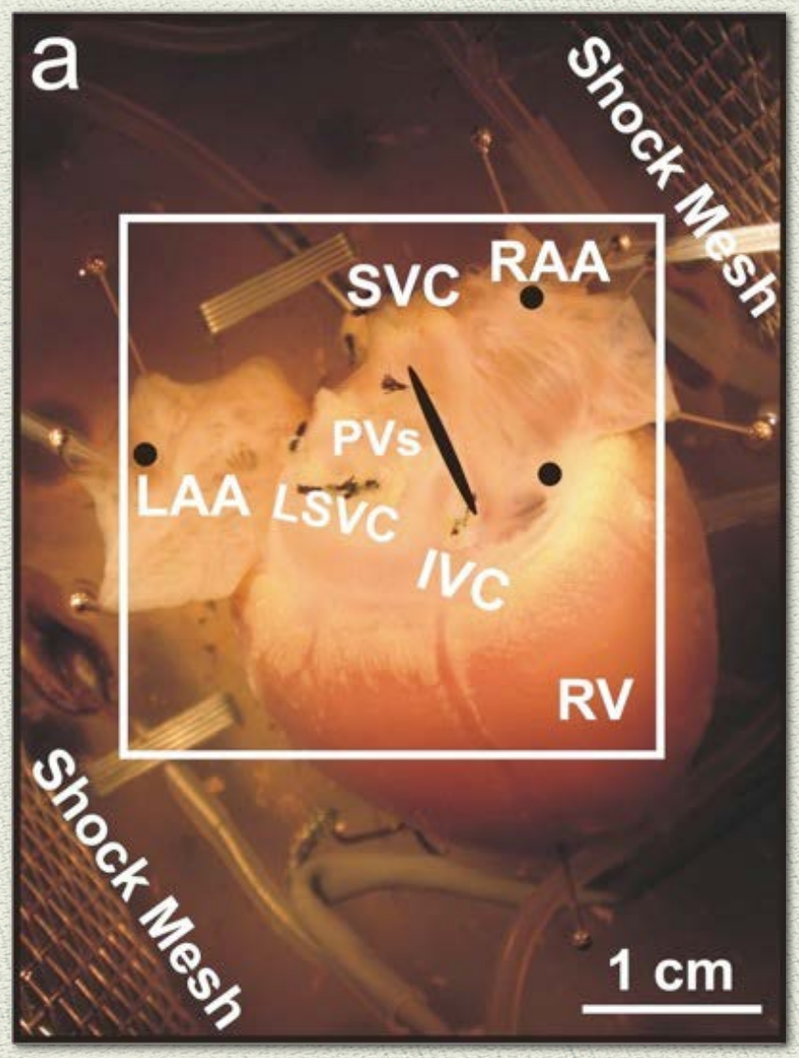
- External cardioversion is painful, necessitating costly anesthesia and careful peri-procedural patient monitoring.

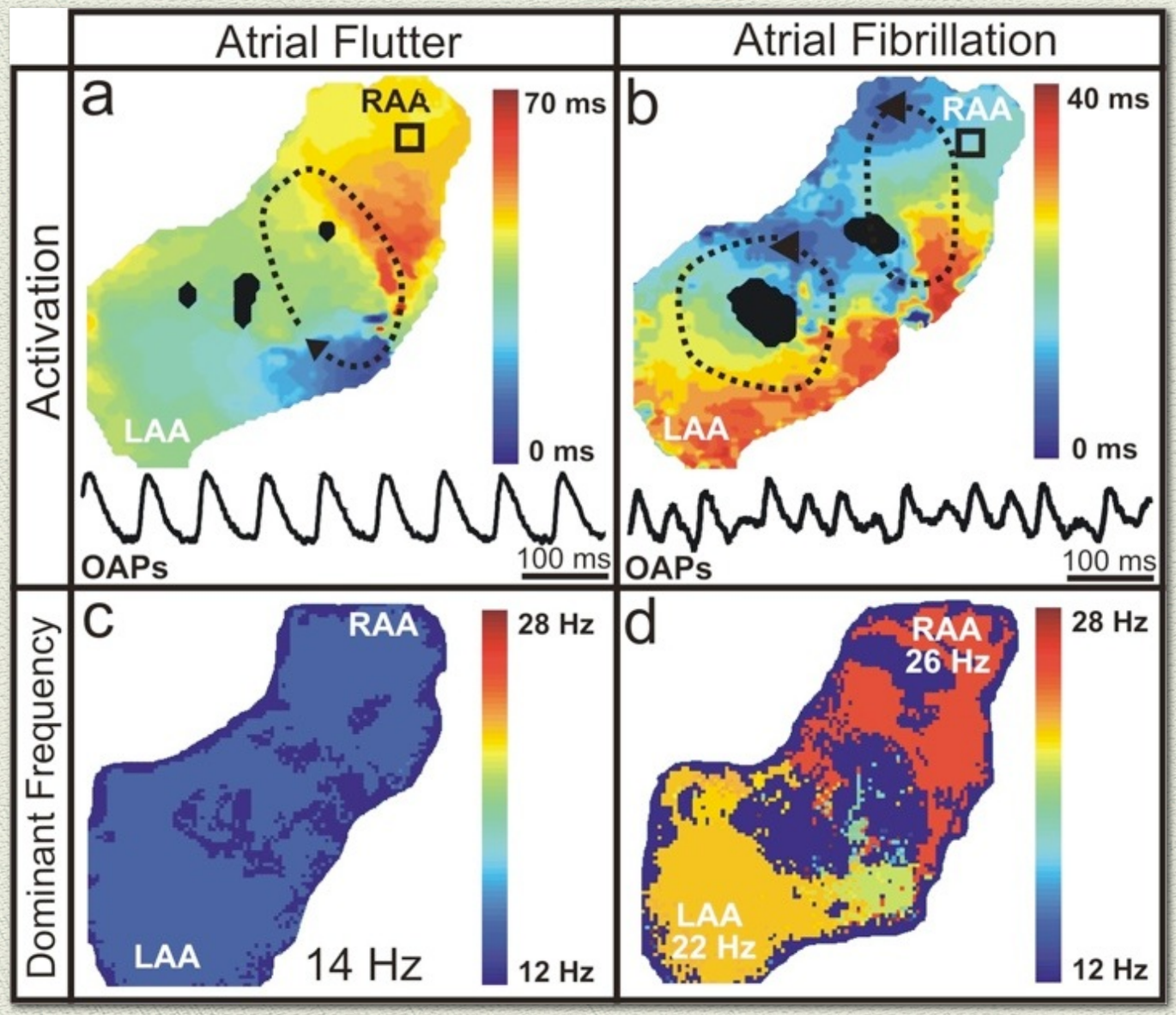


- Previous attempts to develop an implantable atrial cardioverter fell out of favor due to the pain associated with internal cardioversion (3-6 J).

- Geller et al., 2003. Eur Heart J.

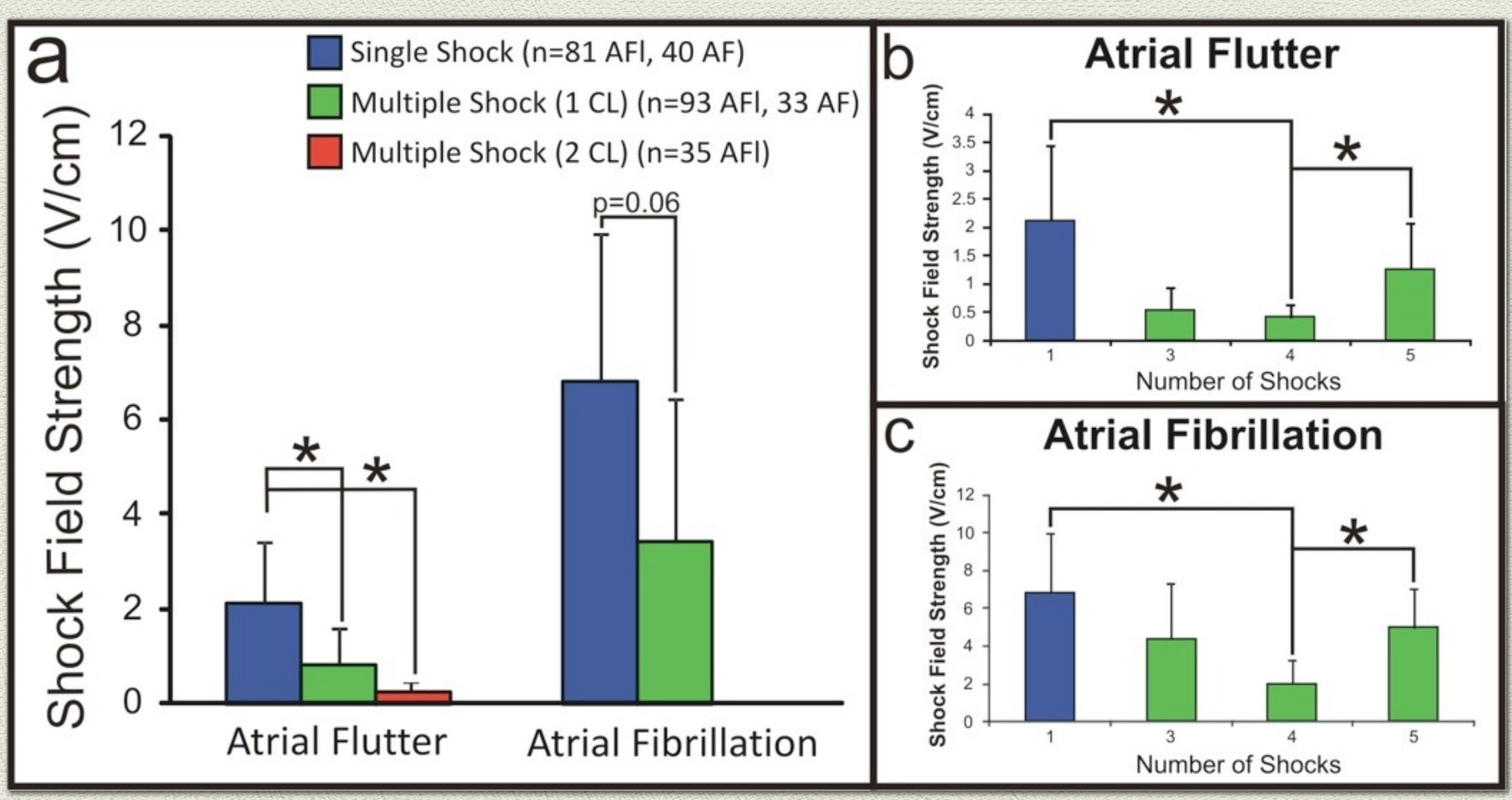
AF and AFI in the rabbit model of atrial tachyarrhythmia





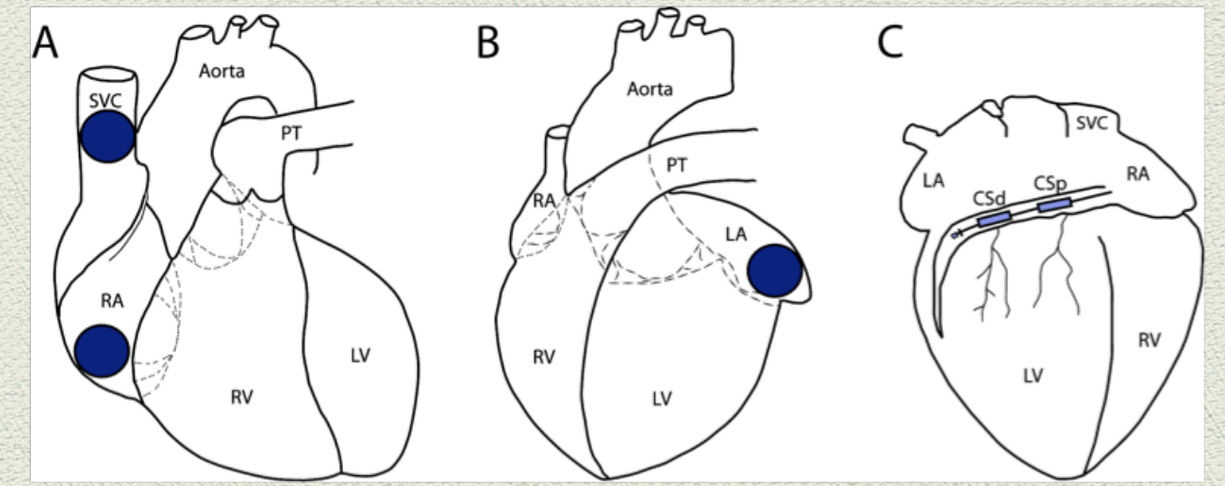
Ambrosi, HRJ, 2011

3-4 pulse therapy is optimal in the rabbit model of AF/AFI



Ambrosi, HR, 2011

In vivo atrial defibrillation study design: Acute canine model

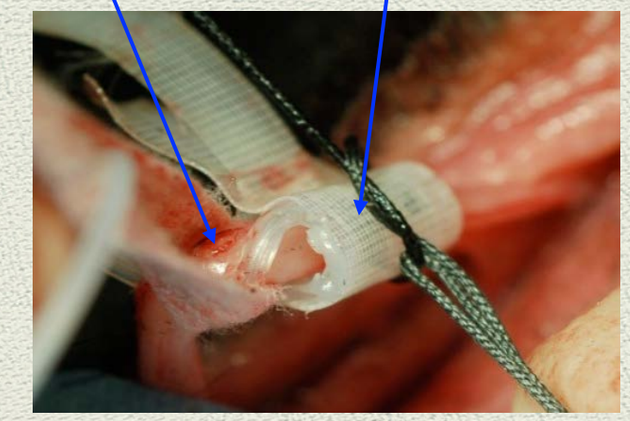


Three vectors:

- SVC--CSd;
- LAA-CSp;
- RAA--LAA

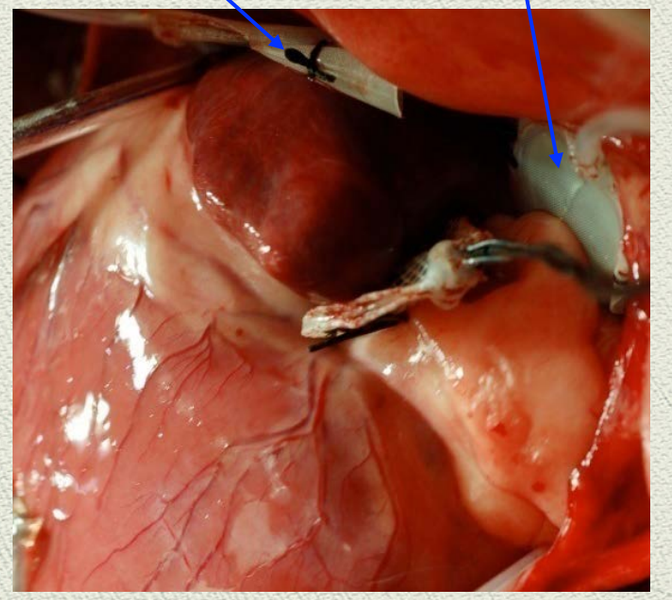
Vagus nerve

Cuff electrode

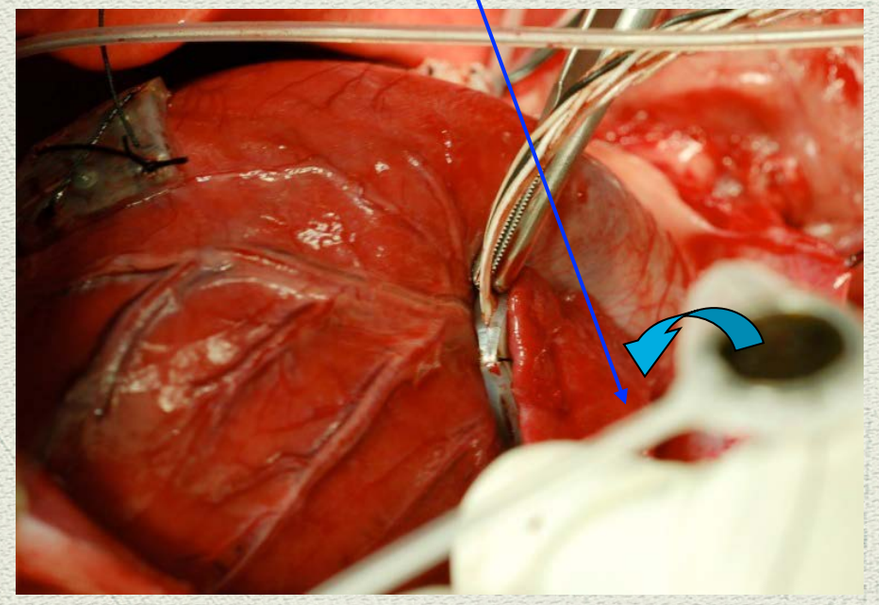


RAA disk electrode

SVC disk electrode



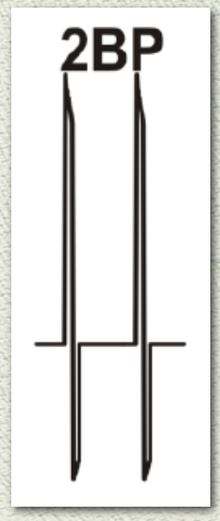
LAA disk electrode



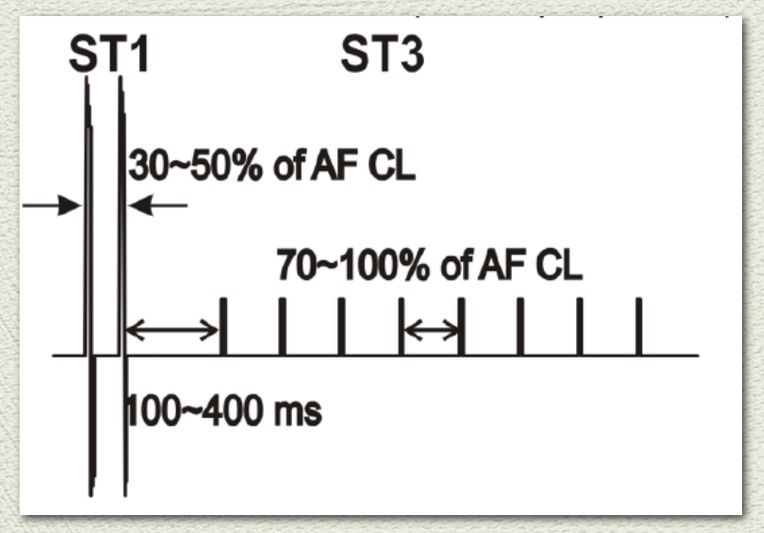
Li, Circ AE, 2012

Multi-stage defibrillation therapies tested in the canine acute AF model

Stage 1: UNPINNING

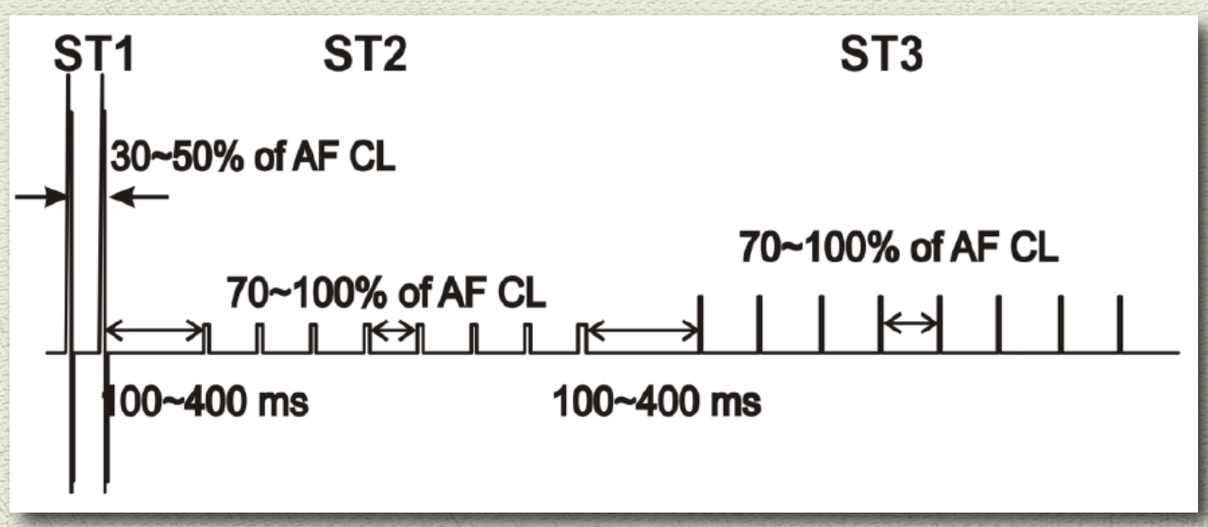


Stage 1: UNPINNING
Stage 3: ANNIHILATION



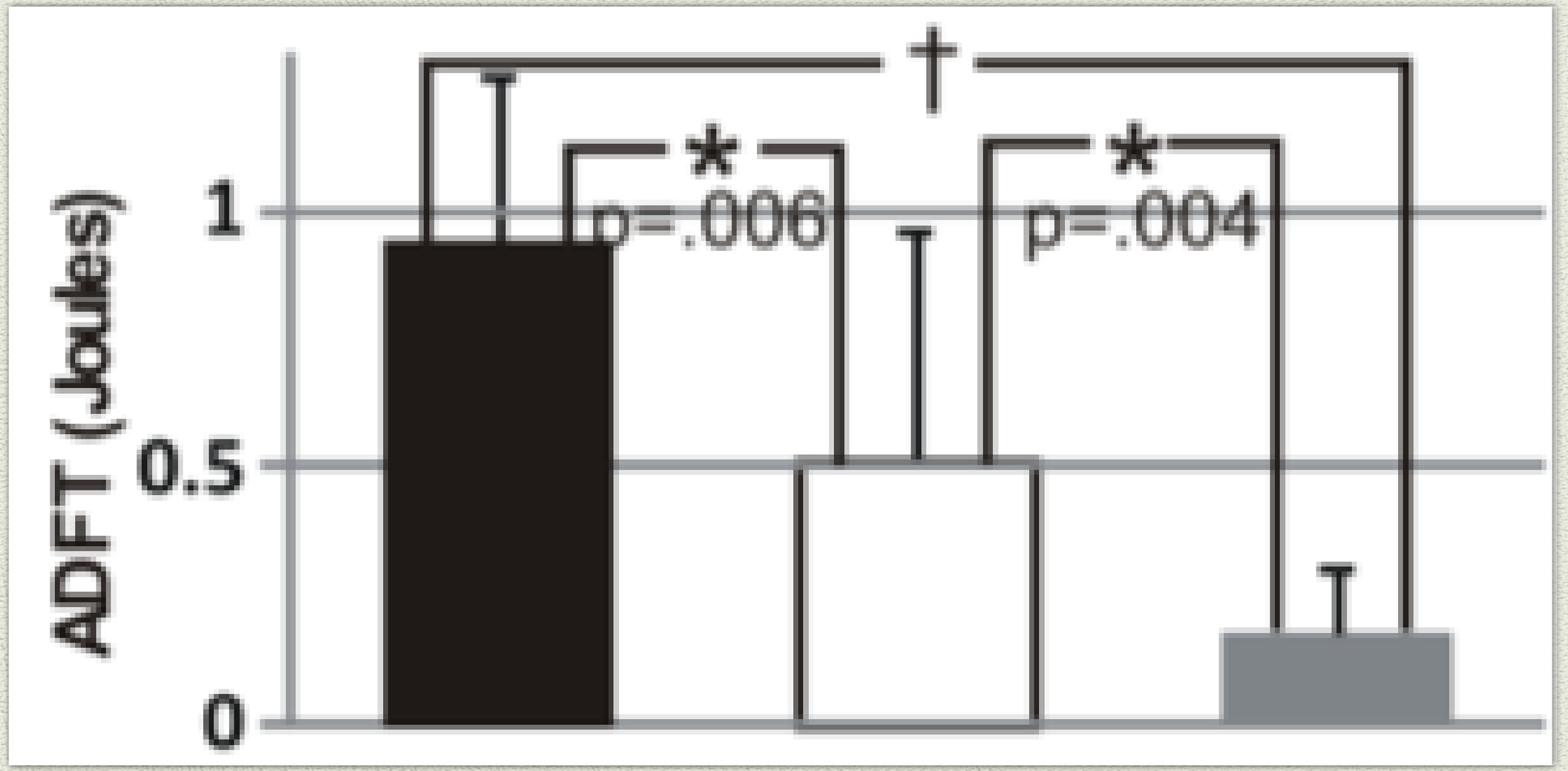
Multi-Stage Therapy

Stage 1: UNPINNING
Stage 2: ANTI-REPINNING
Stage 3: ANNIHILATION



Li, Circ AE, 2012

Multi-stage Electrotherapy Terminates acute AF with lower energy than both multiple pulses or a single shock



Li, Circ AE, 2012

Chronic canine model of AF

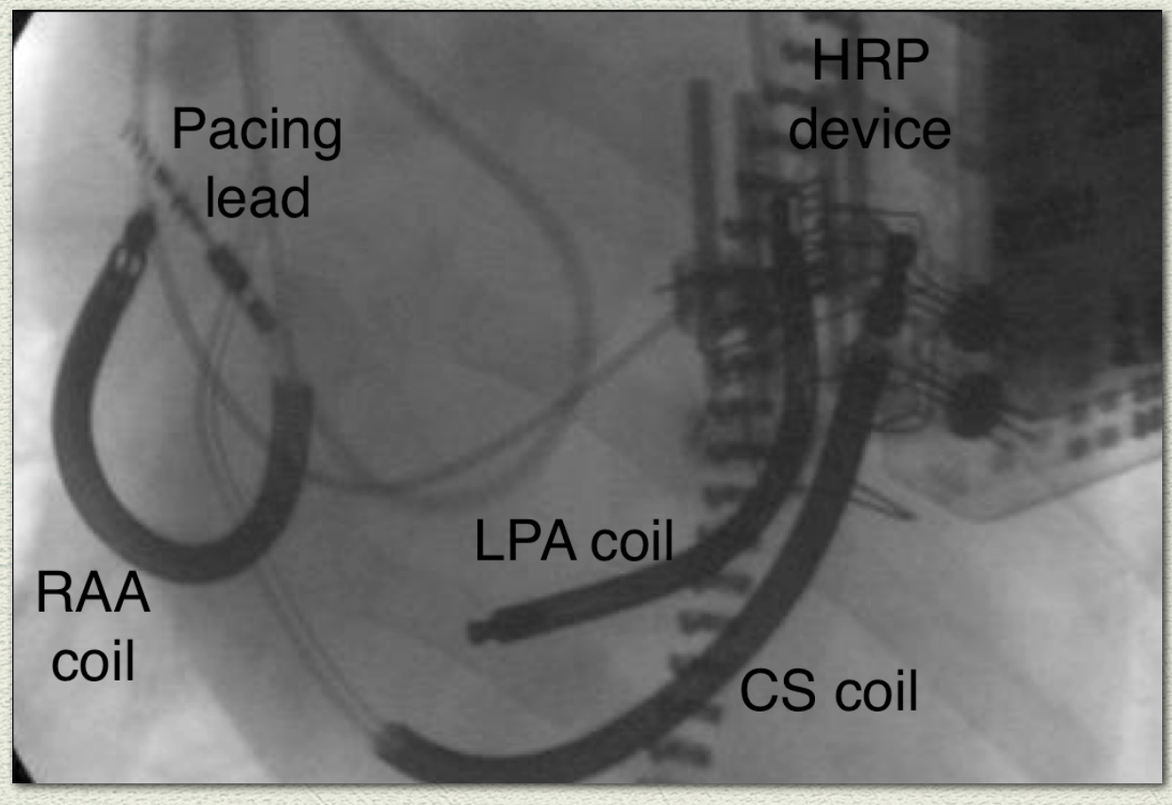
- Test the Three-Stage Electrotherapy in a more clinically relevant model of AF.

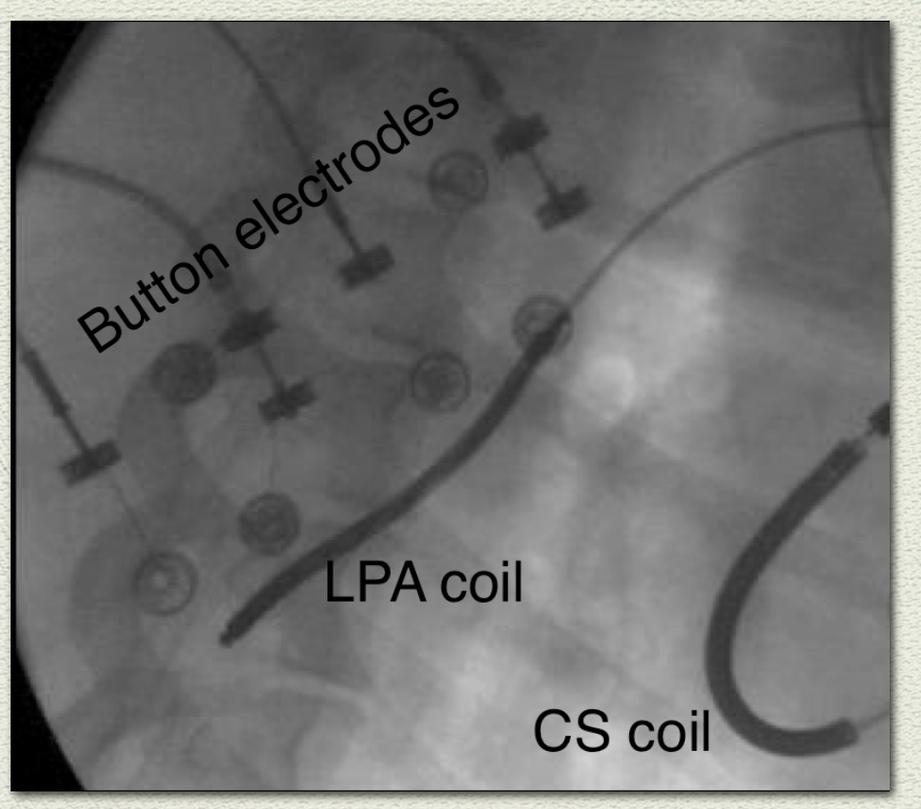
- Develop chronic atrial high rate pacing (HRP) canine model of AF.

- Develop a transvenous lead system to deliver this therapy.

- Limitations: acute AF, open chest configuration

Methods





- Implant high rate pacing device (MDT Entrust ICD with HRP software, connected to MDT 5096 pacing lead).

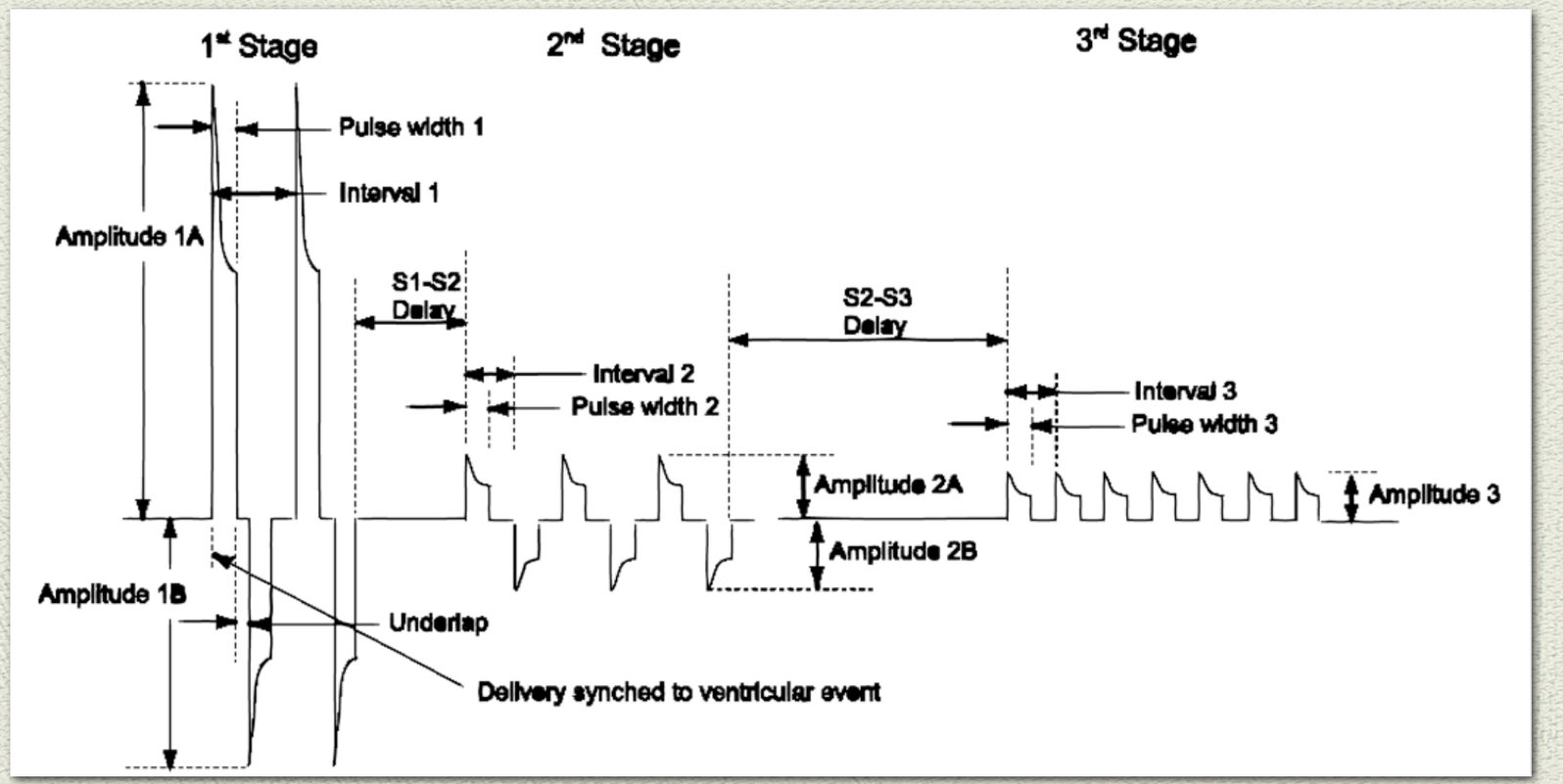
- Implant three defibrillation coils connected to subcutaneous button electrodes (RAA, CS, LPA).

Janardhan, JACC, 2014

LVD in a canine model of Persistent AF

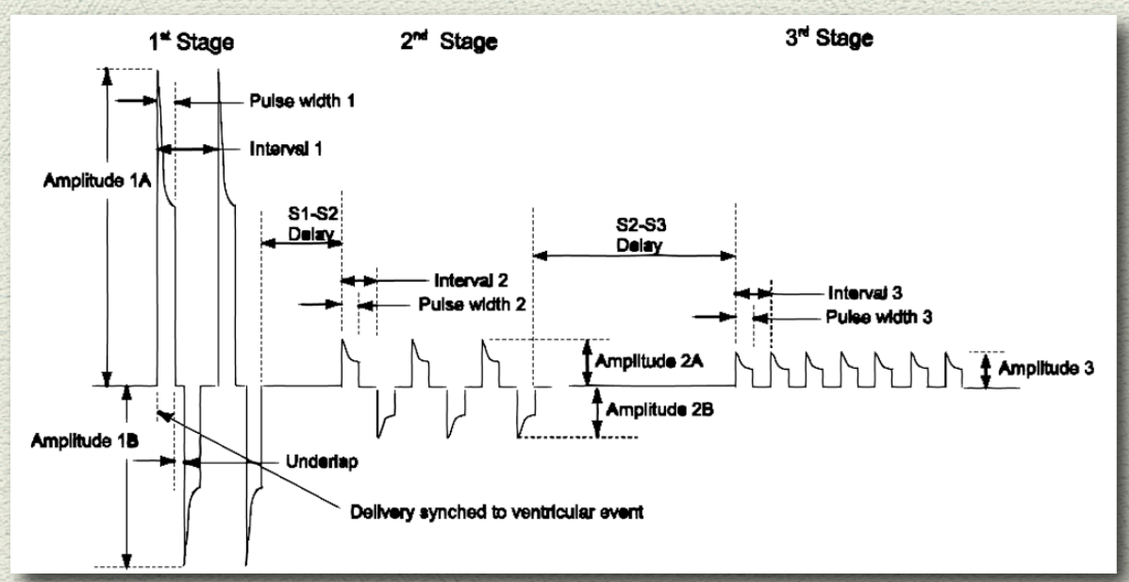
WEEK 4+: Defibrillation Study

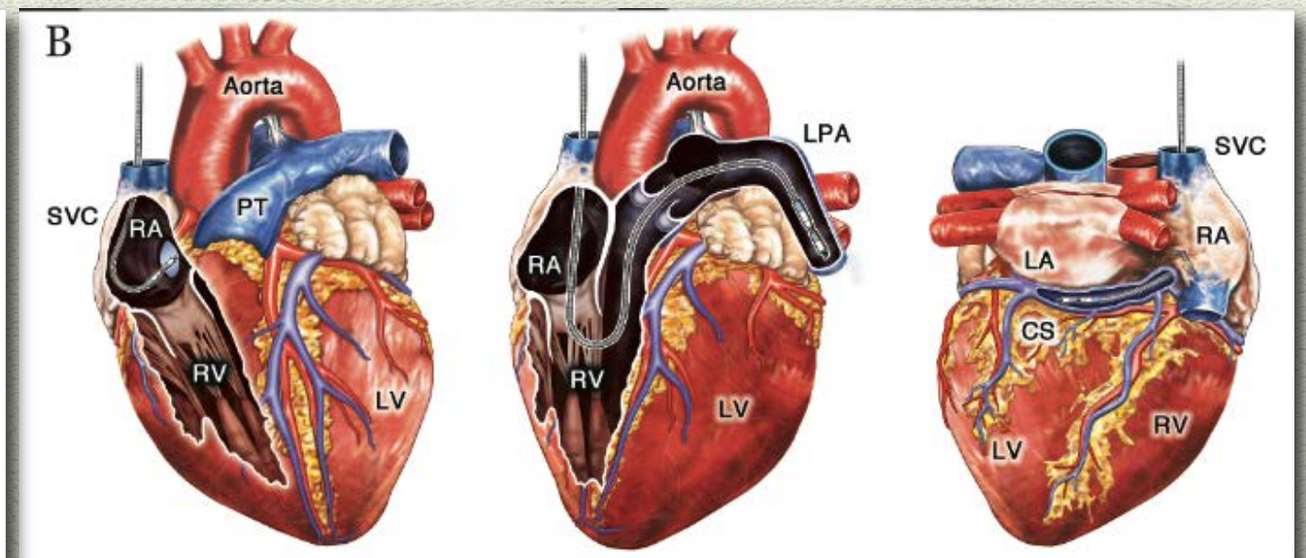
1. Intubation, mechanical ventilation with isoflurane
2. Determination of AERP, Ventricular Shock Excitation Threshold (SET) via each vector
3. AF induction via 50 Hz burst pacing
4. Evaluation of defibrillation electrotherapies for termination of AF

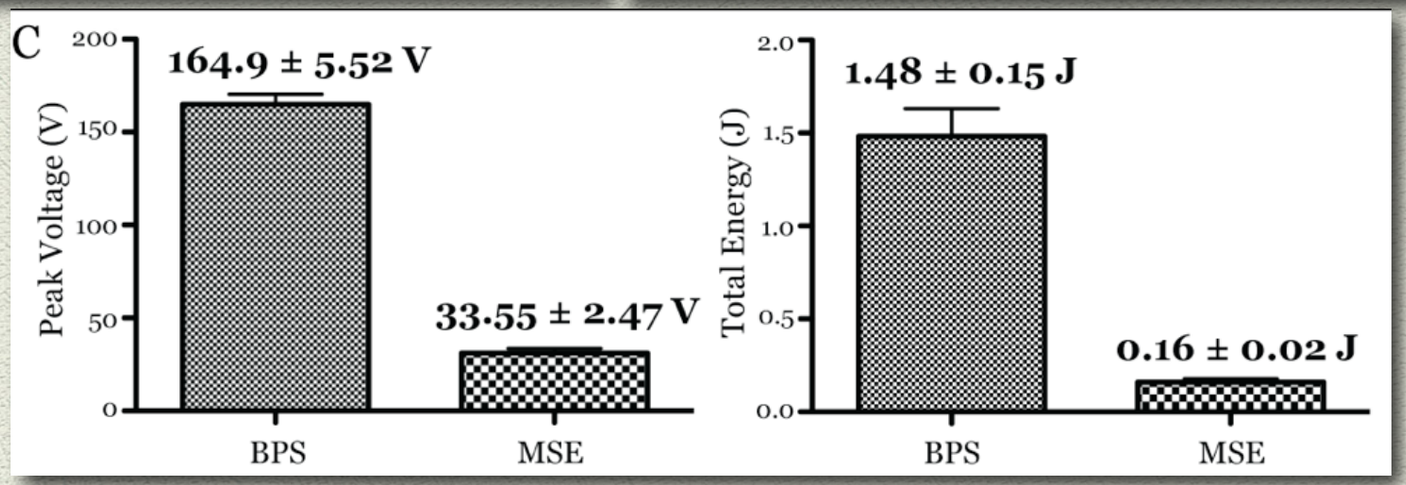


Janardhan, JACC, 2014

Low energy atrial defibrillation







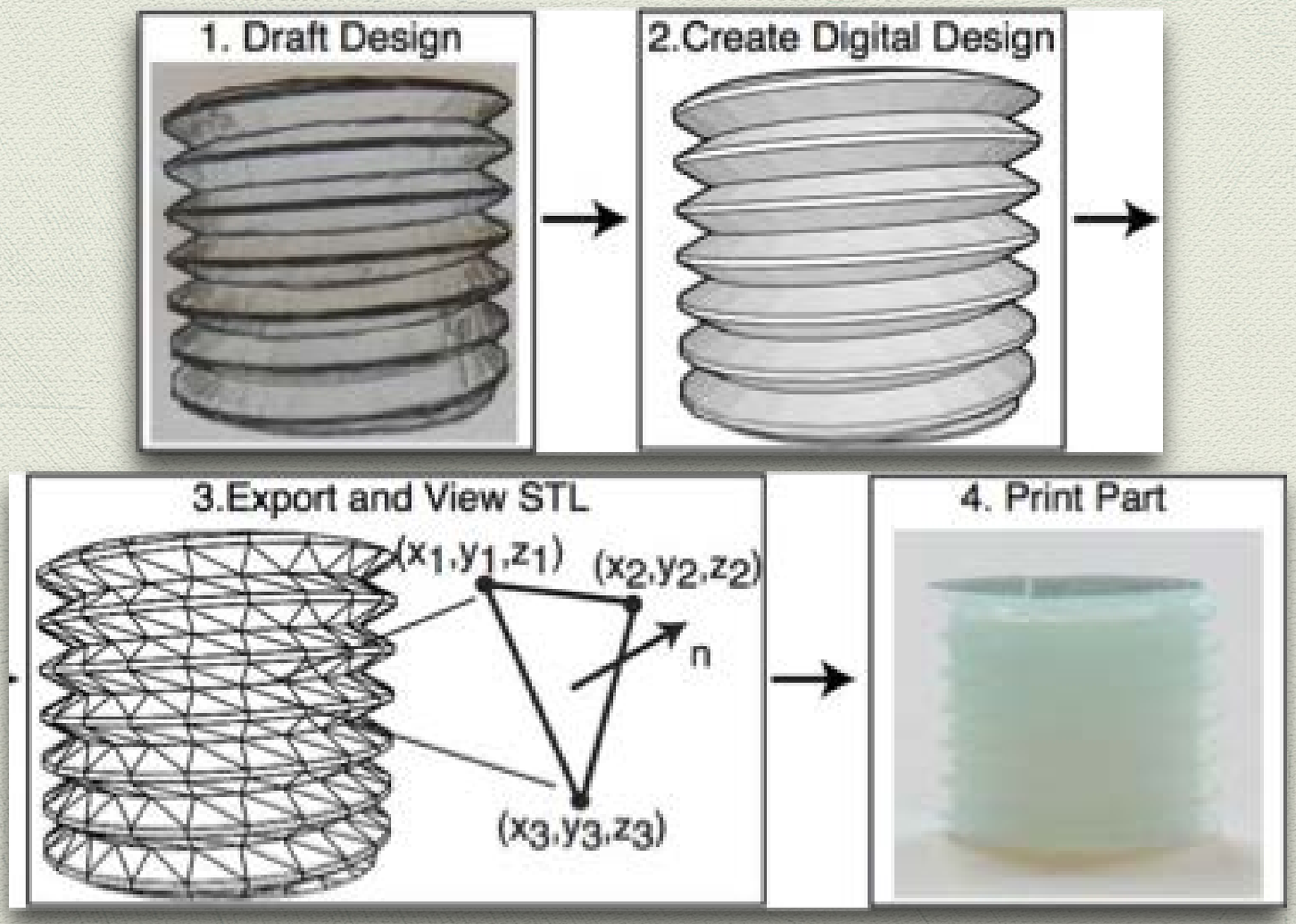
- Significantly lowers the atrial defibrillation threshold compared to a single biphasic shock in a canine model of persistent AF: 0.16 ± 0.02 J vs 1.48 ± 0.15 J ($p<0.001$) or 33.5 ±2.5 V vs 164 ±5.5 V ($p<0.001$).
- Can be delivered through a transvenously implanted lead system.

Cardialen, Inc.

Outline

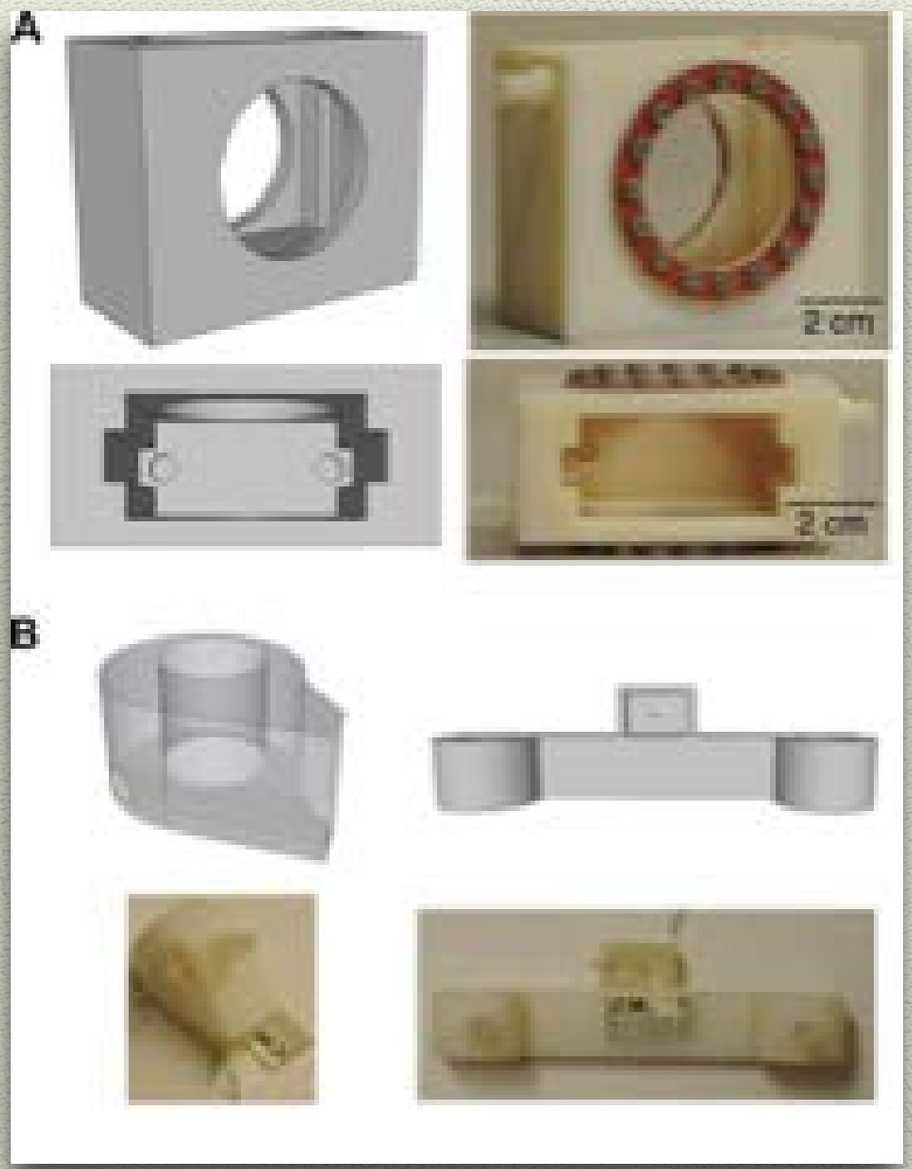
- Engines of Innovation: Innovative University
- Biomedical Research Enterprise
- Therapy for Cardiac Arrhythmias
- Stretchable and flexible electronics
- Patient-specific therapies

A digital design of a screw thread converted to a stereolithography (STL) file and printed.



Sulkin M S et al. Am J Physiol Heart Circ Physiol 2013; 305: H1569-H1573

Digital designs and 3-D printed objects for physiology experiments

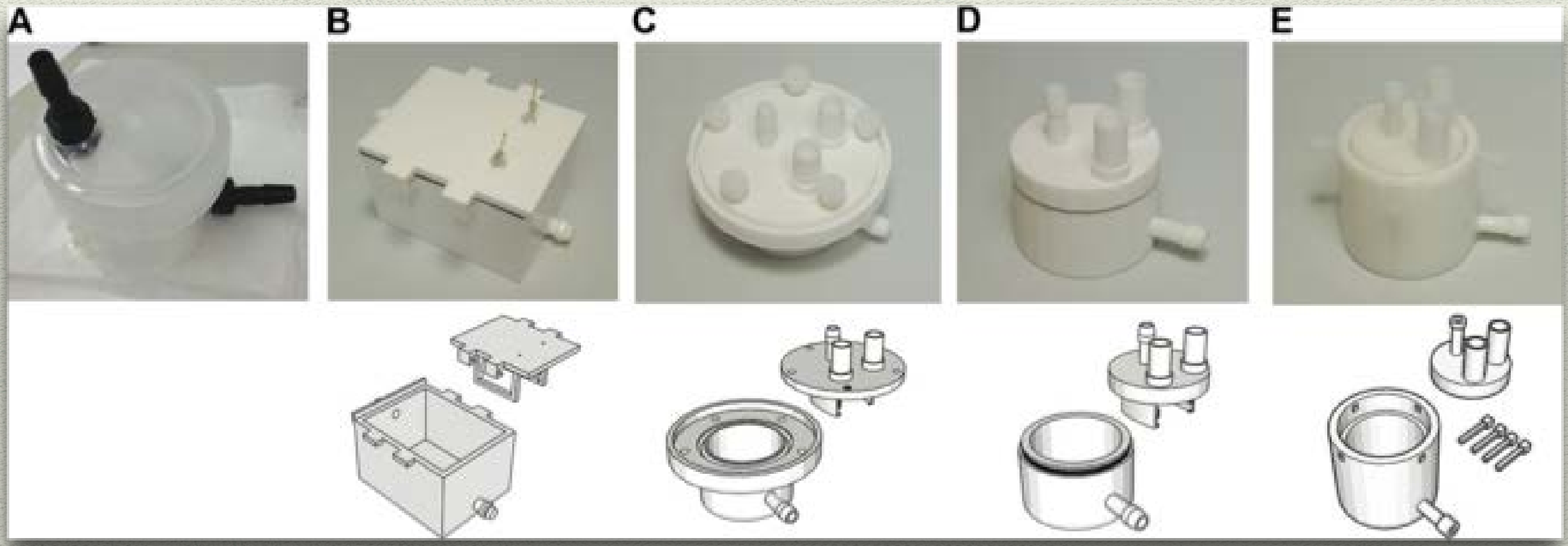


D

	3D Printed	Industry
Tissue Chamber	$145.00	$962.82*
Pt-Ir Electrode 2x	$13.48	$912.00**
Micropositioner 2x	———	$1,556.76***
Tissue Restrainer	$0.35	NA
Total	$158.83	$3,431.58

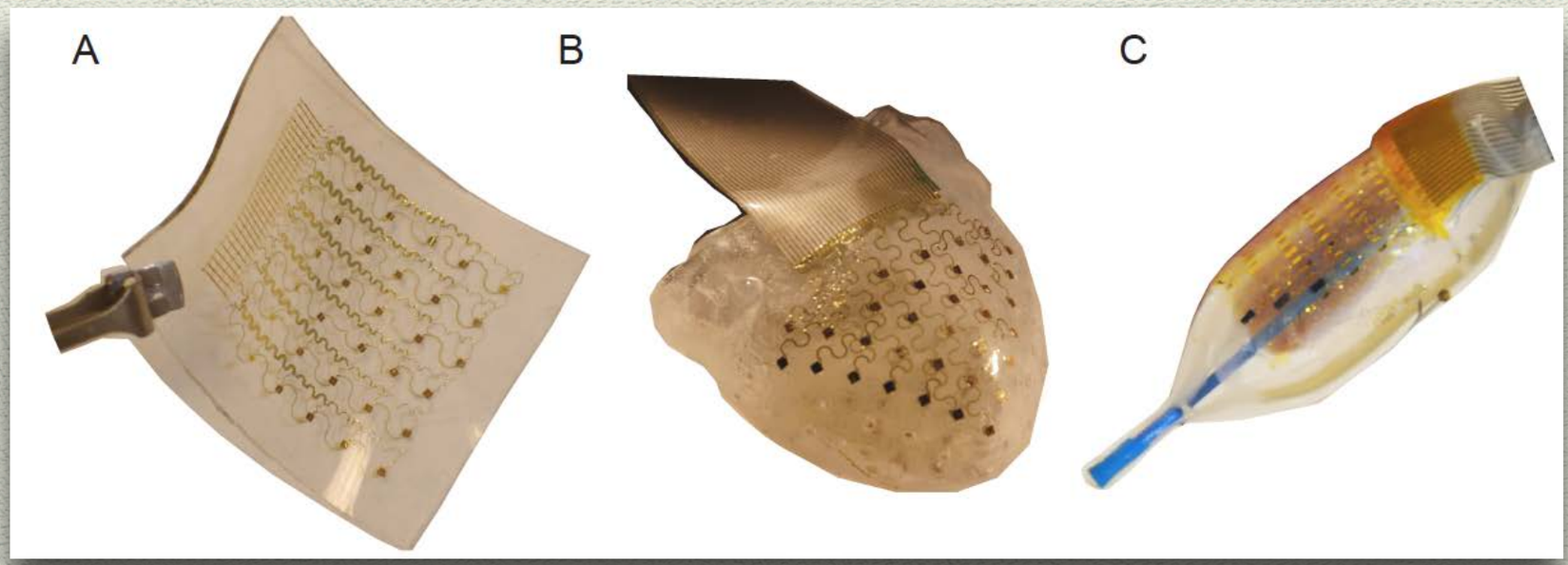
Sulkin M S et al. Am J Physiol Heart Circ Physiol 2013; 305: H1569-H1573

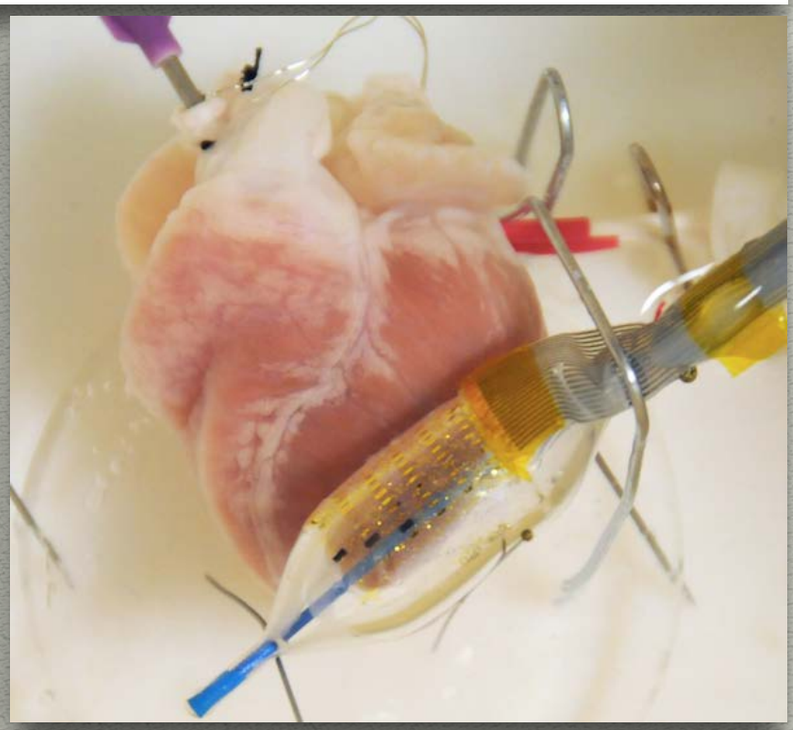
Prototyping a CLARITY chamber.



Sulkin M S et al. Am J Physiol Heart Circ Physiol 2013;305:H1569-H1573

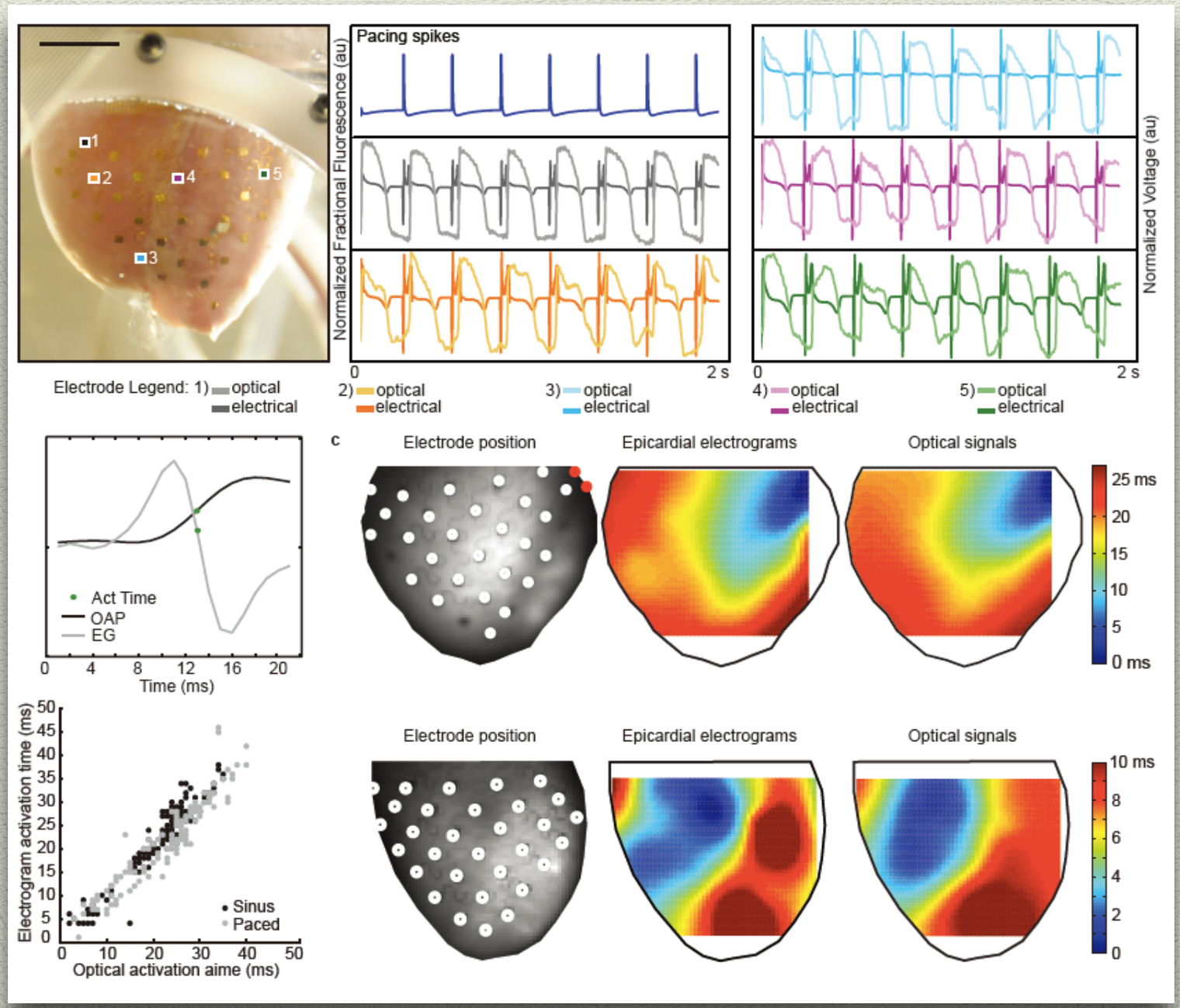
Stretchable/Flexible Organ Conformal Electronics





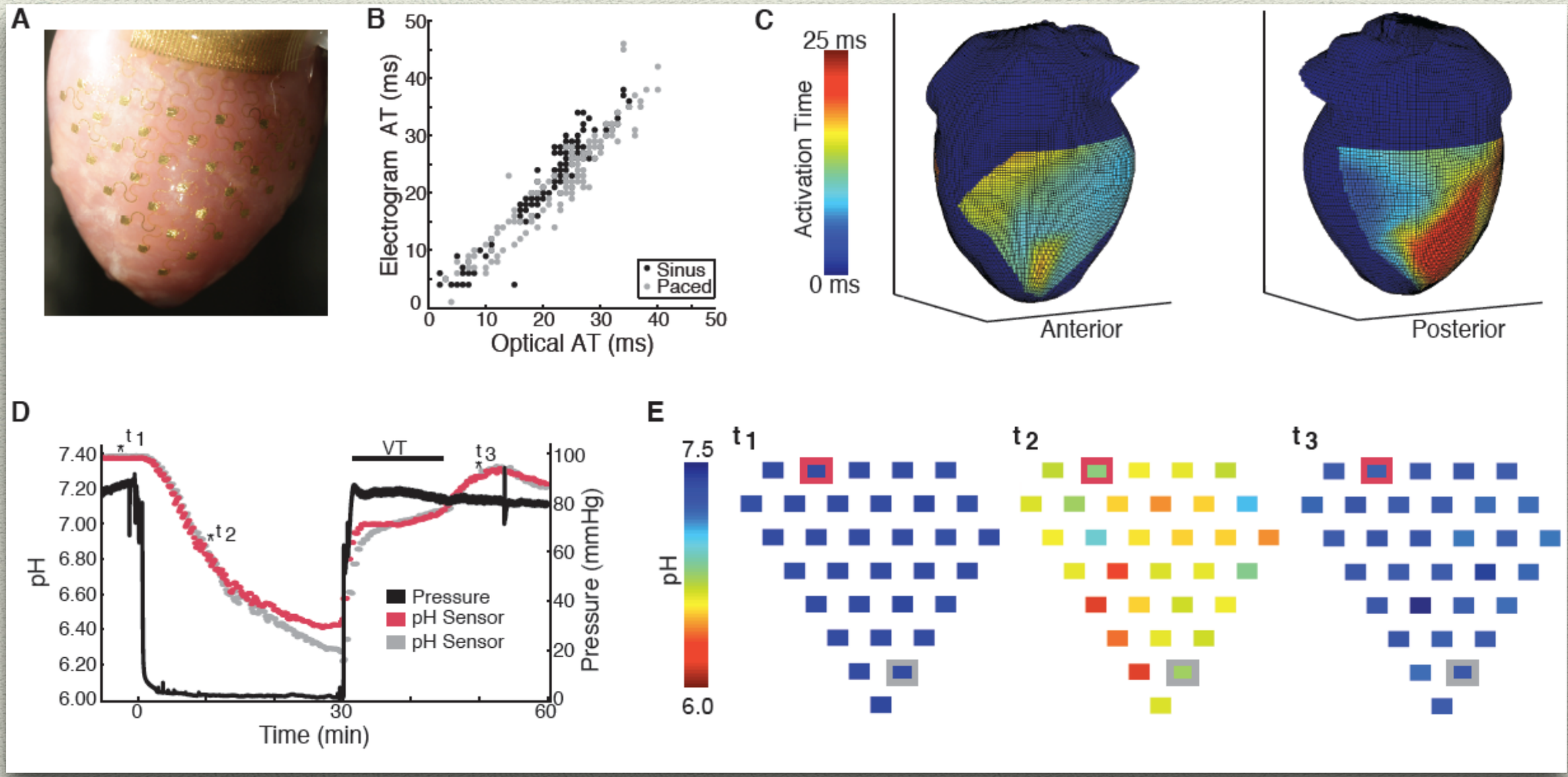
Xu et al, Nature Communications, 2014

Electrical cardiac mapping and pacing



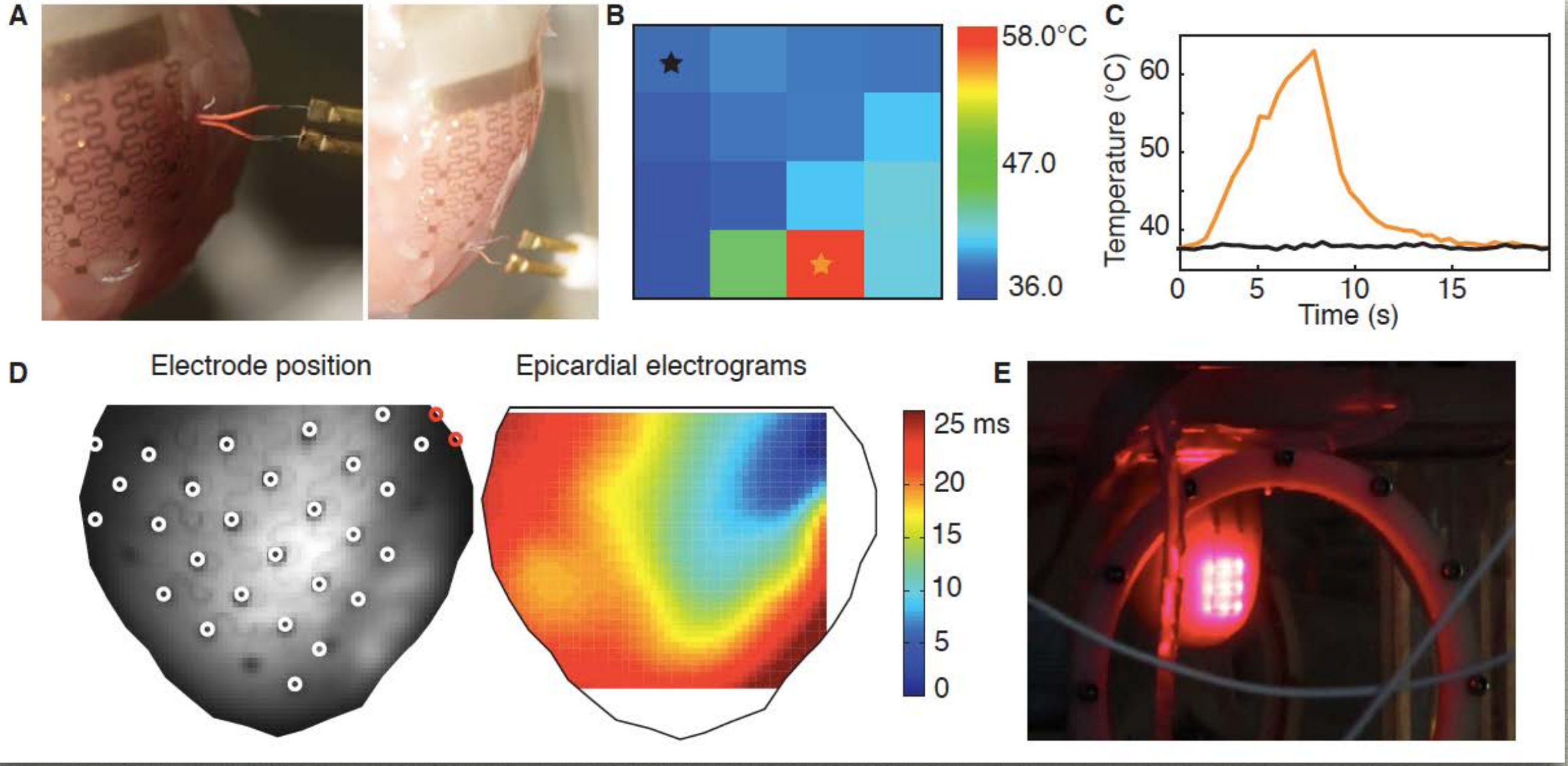
Xu et al, Nature Communications, 2014

Metabolic imaging



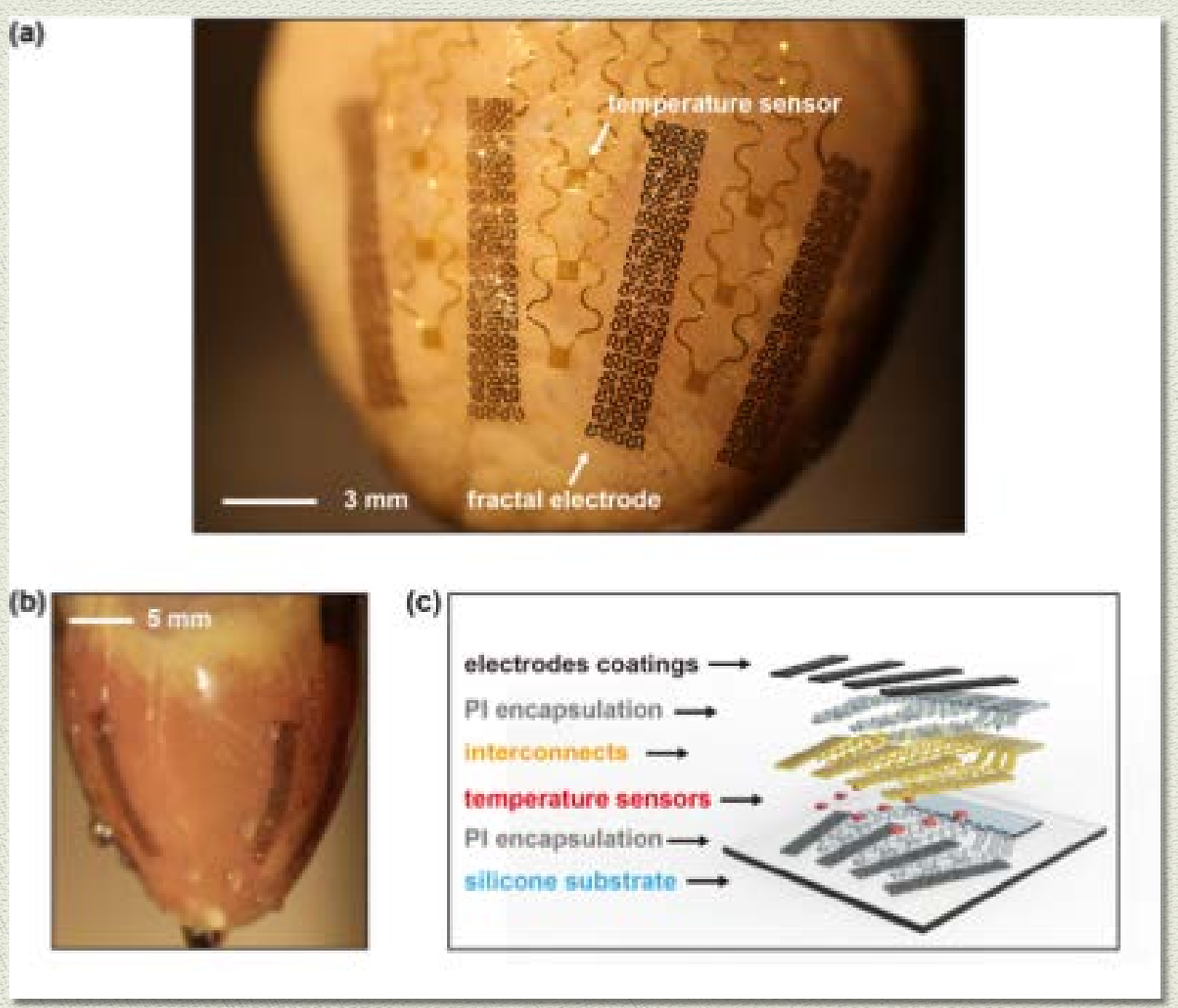
Xu et al, Nature Communications, 2014

Real-time therapy monitoring: temperature and optical spectroscopy



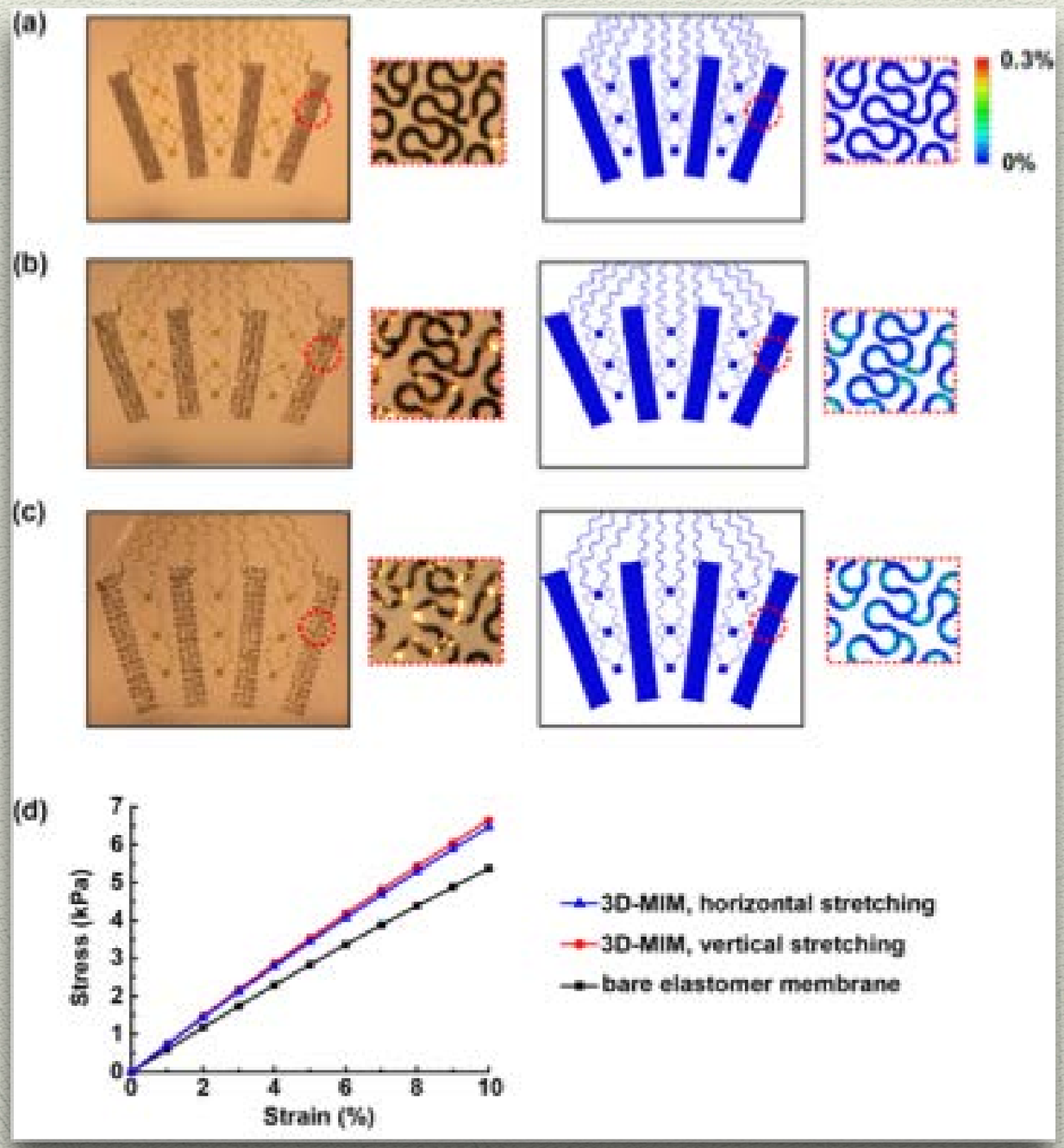
Xu et al, Nature Communications, 2014

Design of a stretchable/flexible defibrillator with fractal electrodes



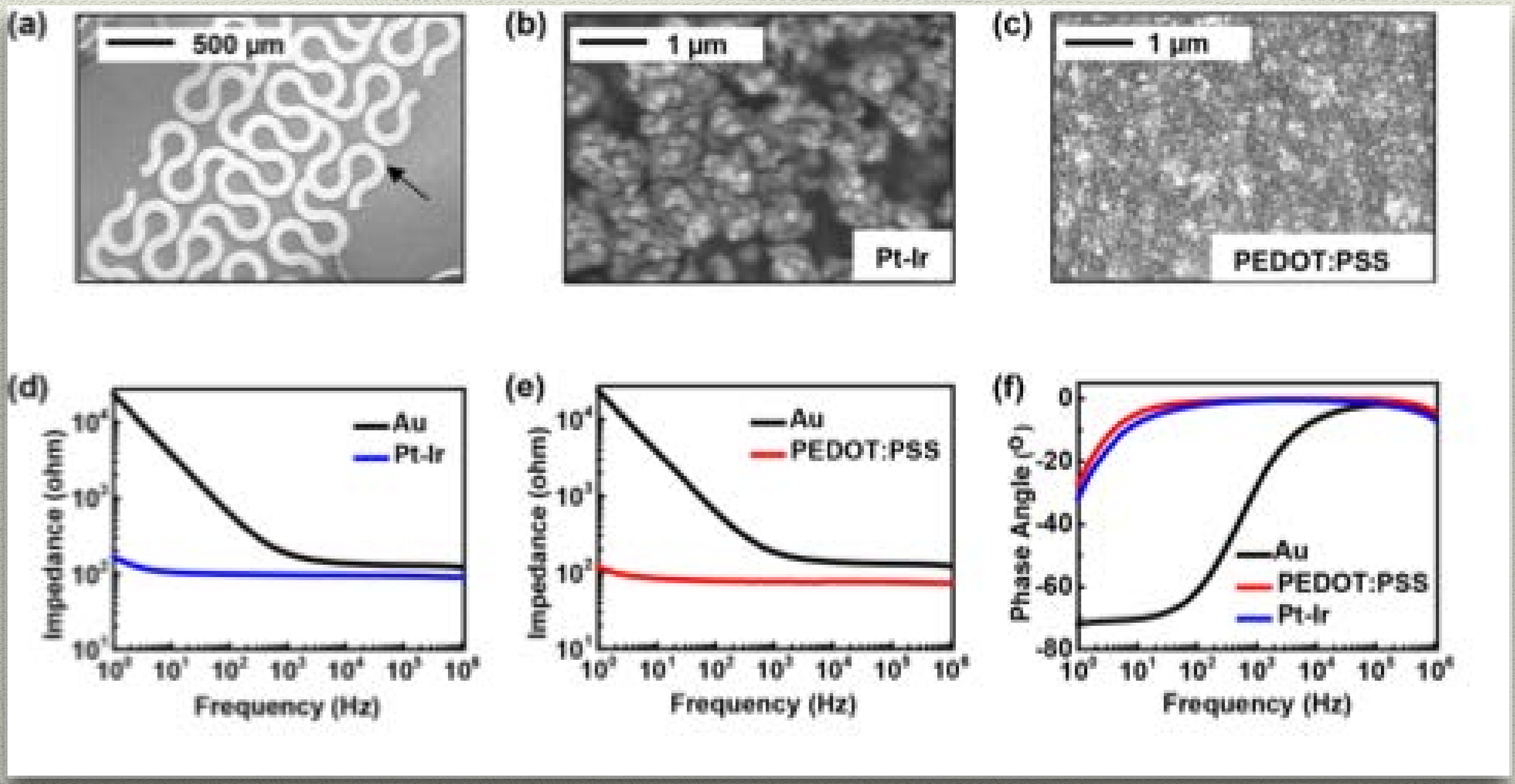
Xu et al., Adv. Mater., 2015

The distribution of maximum principal strain



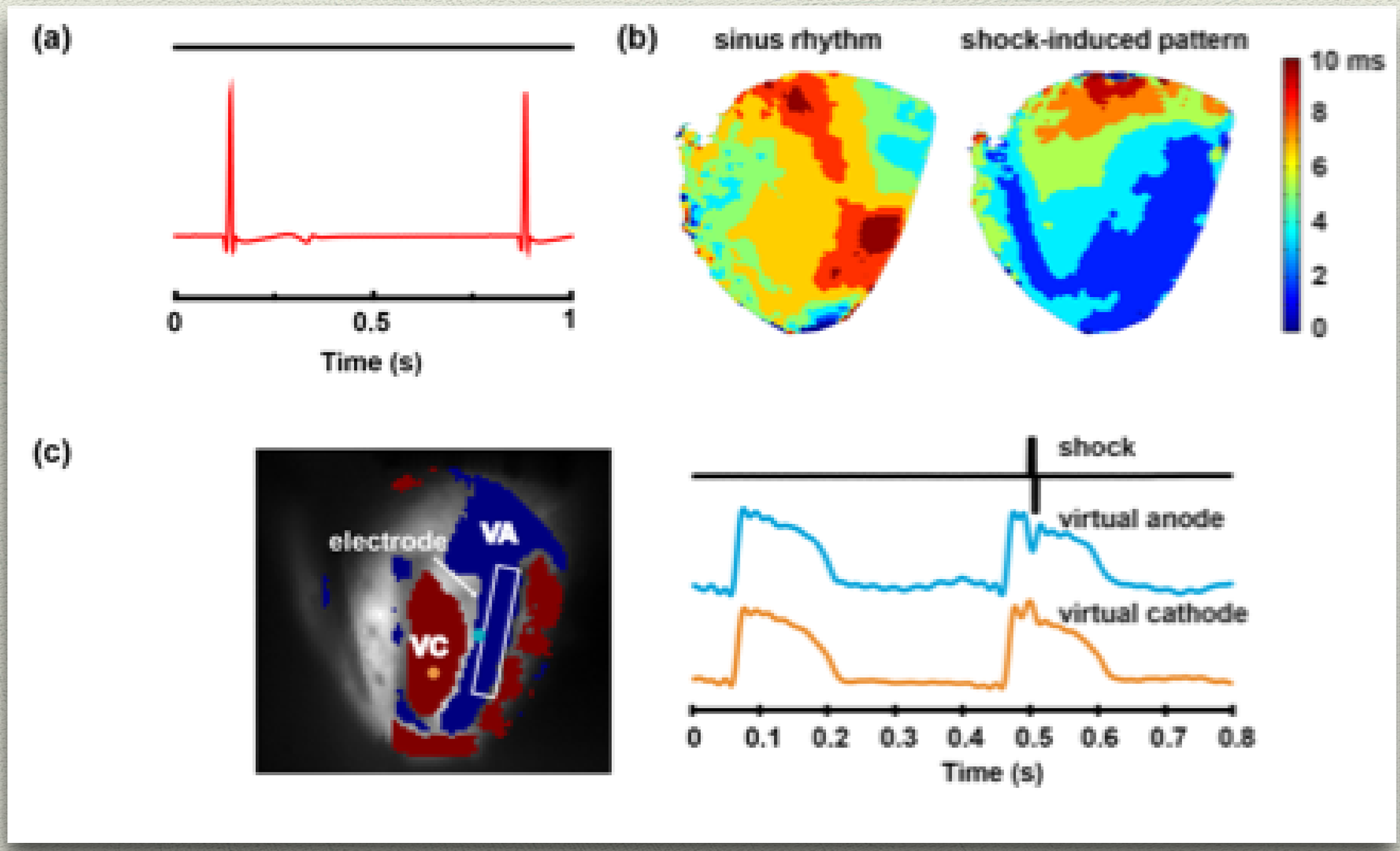
Xu et al., Adv. Mater., 2015

SEM images and Bode magnitude plots of electrochemical impedance spectroscopy data for Au base and nano-textured Pt-Ir coated electrodes



Xu et al., Adv. Mater., 2015

Electrograms, activation maps and virtual electrodes recorded/induced by the device

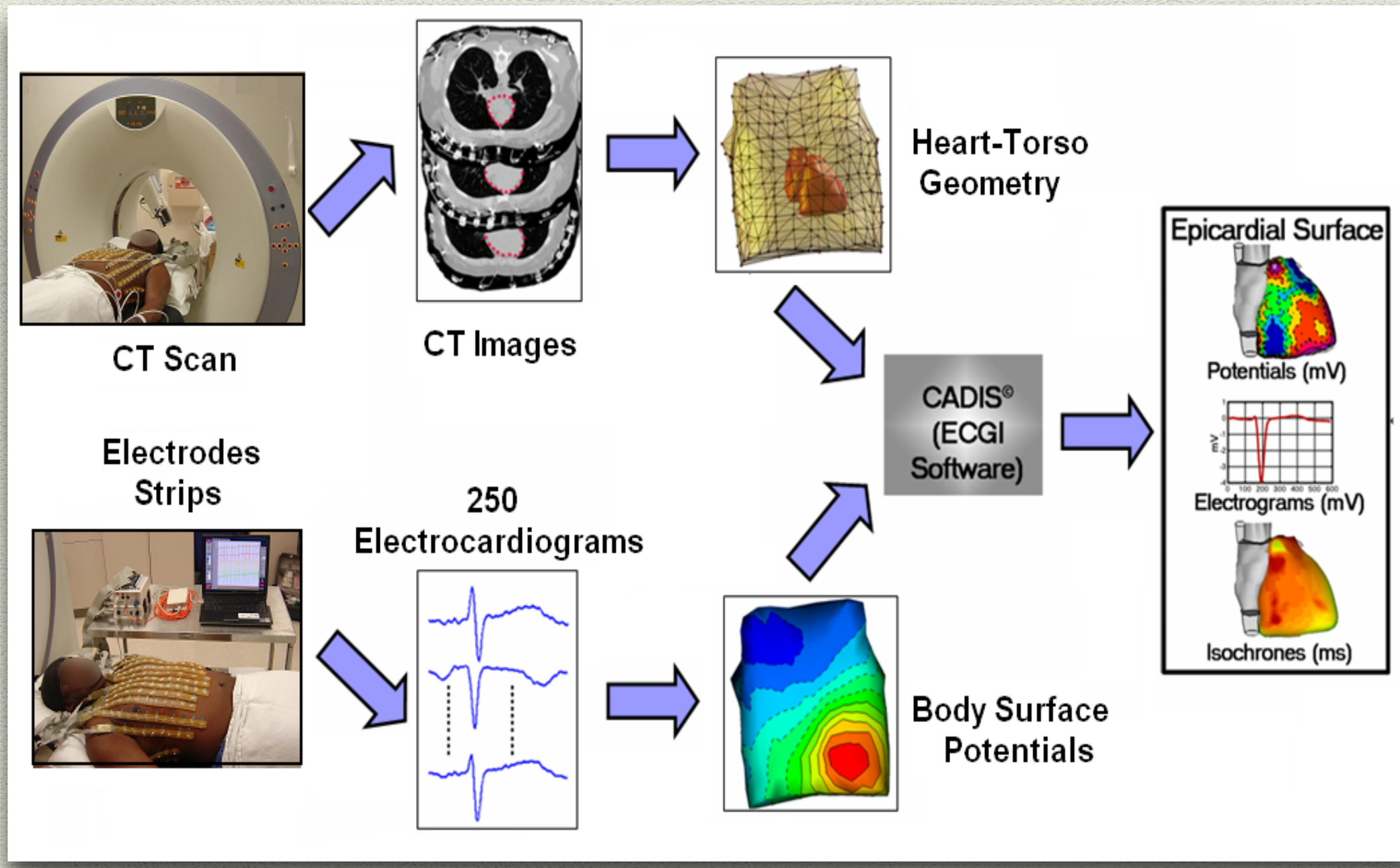


Xu et al., Adv. Mater., 2015

Outline

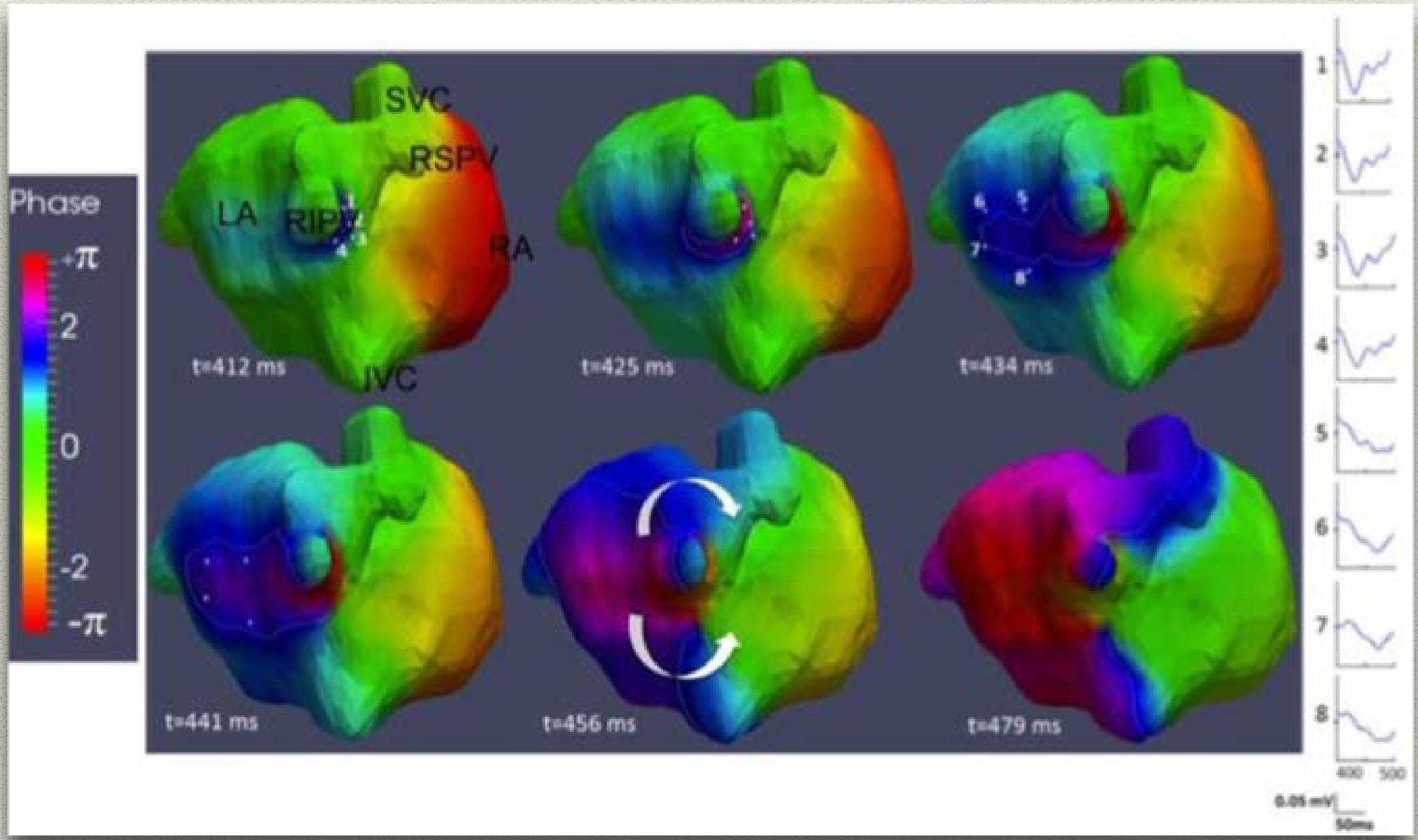
- Engines of Innovation: Innovative University
- Biomedical Research Enterprise
- Therapy for Cardiac Arrhythmias
- Stretchable and flexible electronics
- Patient-specific therapies

Rudy: ElectroCardiographic Imaging (ECGi)



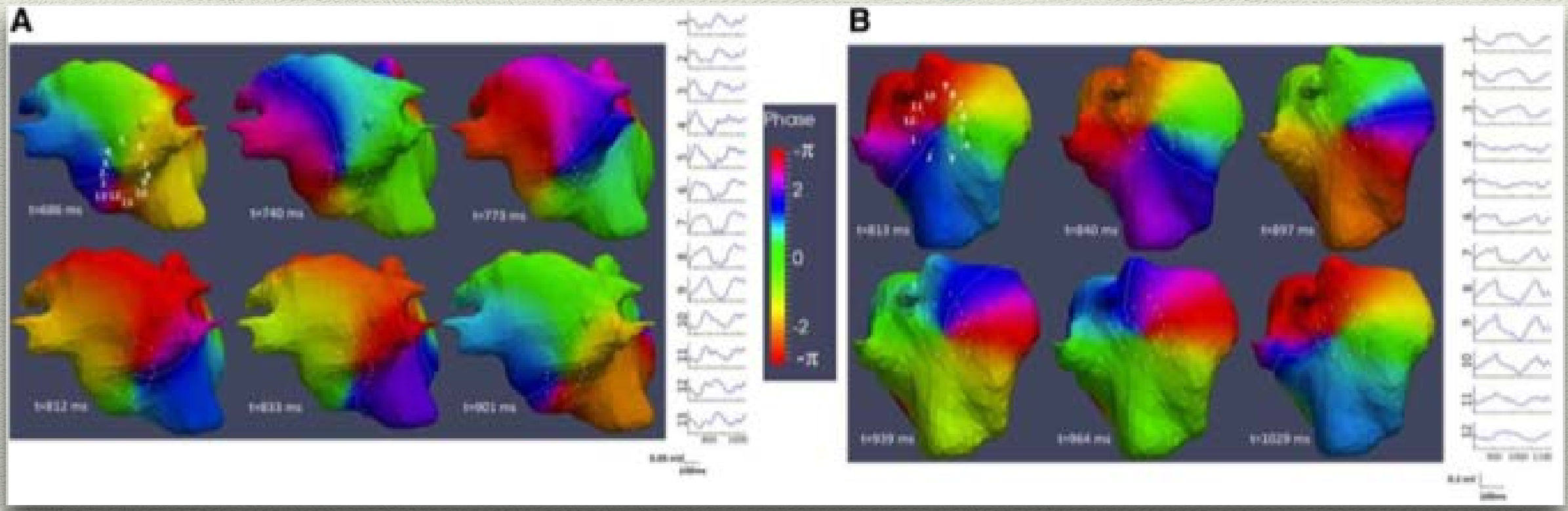
Rudy et al, Nature Medicine, 10:422-428, 2004; PNAS 2006;103:6309-6314.

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



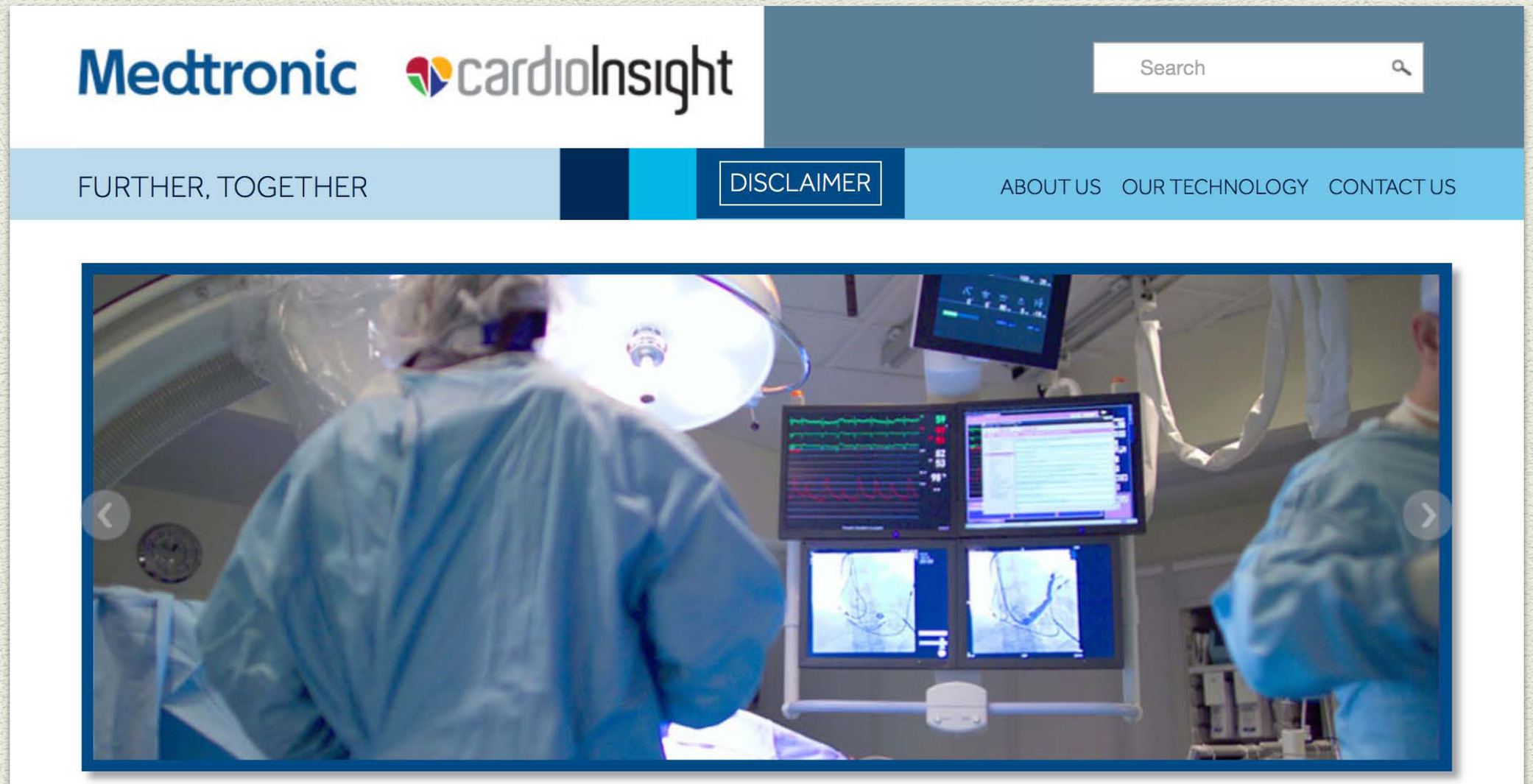
Haissaguerre M et al. Circulation. 2014;130:530-538

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

CardioInsight, Inc.

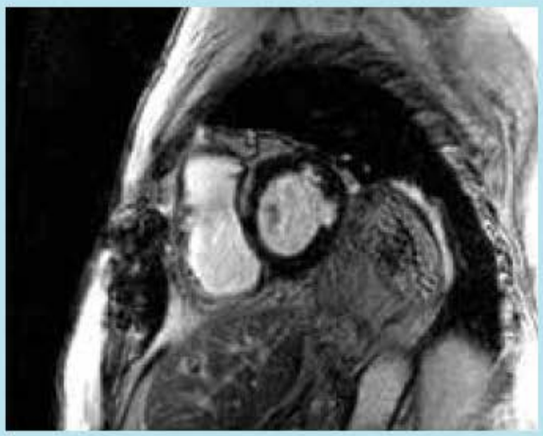


CardioInsight has developed a novel, non-invasive advanced cardiac mapping system to map electrical disorders of the heart. The Company's ECVUE™ system is the first, non-invasive mapping system to provide simultaneous, 3D, multi-chamber mapping and localization of cardiac arrhythmia mechanisms.

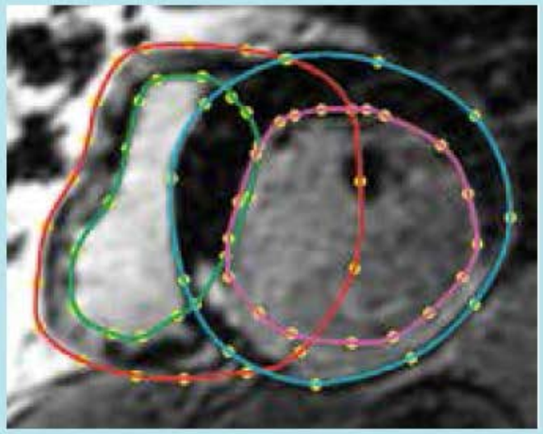
Trayanova: Your Personal Heart

Trayanova NA. IEEE Spectrum, 2014

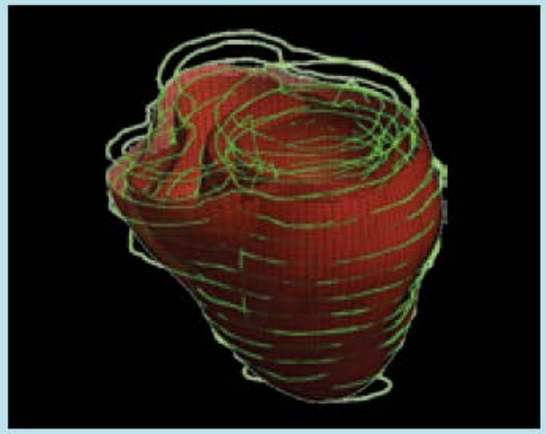
Patient-specific heart anatomy: Making the Mock-Up



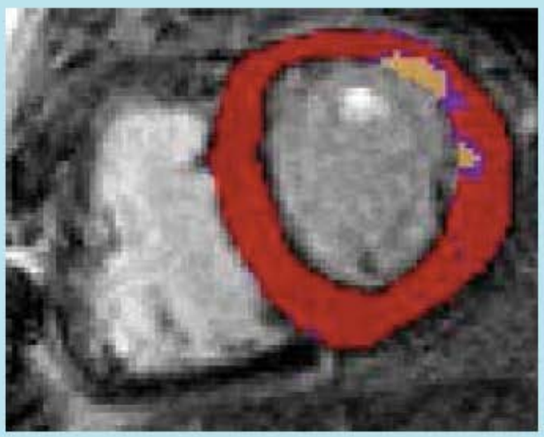
1 **TAKE MRI SCANS** of the patient's heart.



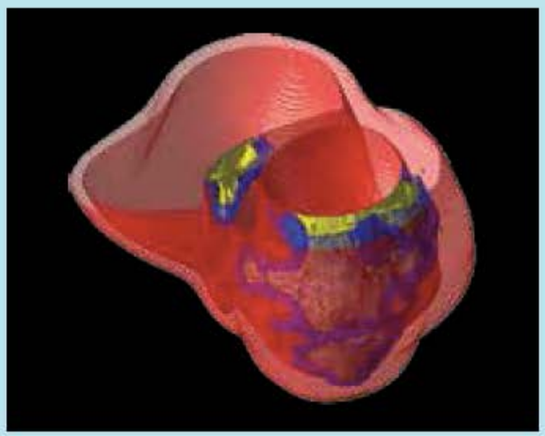
2 **USE IMAGE-PROCESSING TOOLS** to locate the walls of the heart's chambers.



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].

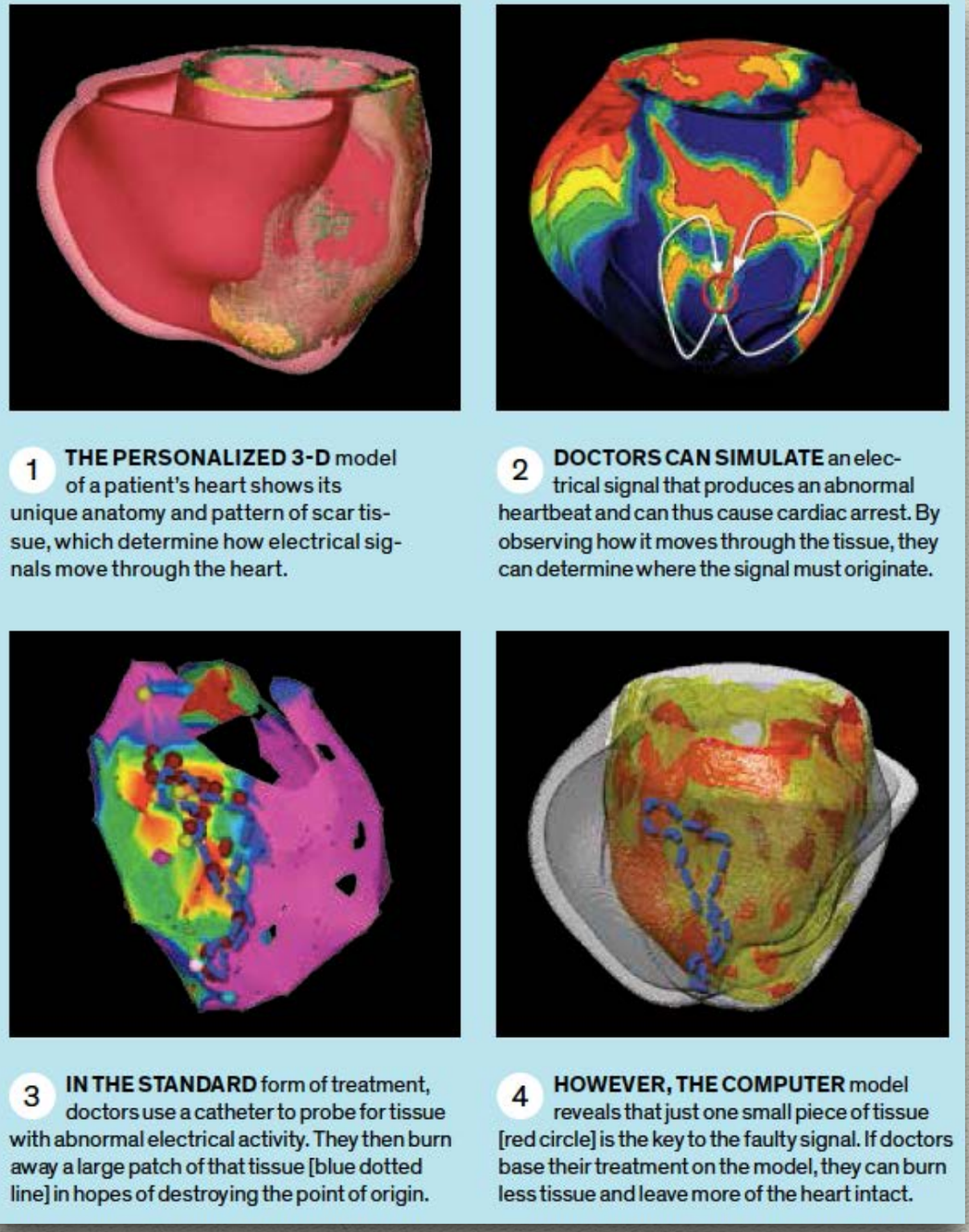


5 **OVERLAY THAT UNIQUE** pattern of scar tissue on the 3-D model.

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.

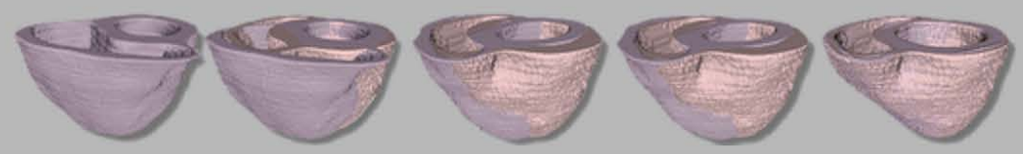
4 **HOWEVER, THE COMPUTER** model reveals that just one small piece of tissue [red circle] is the key to the faulty signal. If doctors base their treatment on the model, they can burn less tissue and leave more of the heart intact.

Trayanova NA, IEEE Spectrum, 2014

CardioSolv, Inc.

cardiosolv
ABLATION TECHNOLOGIES

HOME ABOUT TEAM INVESTORS CONTACT



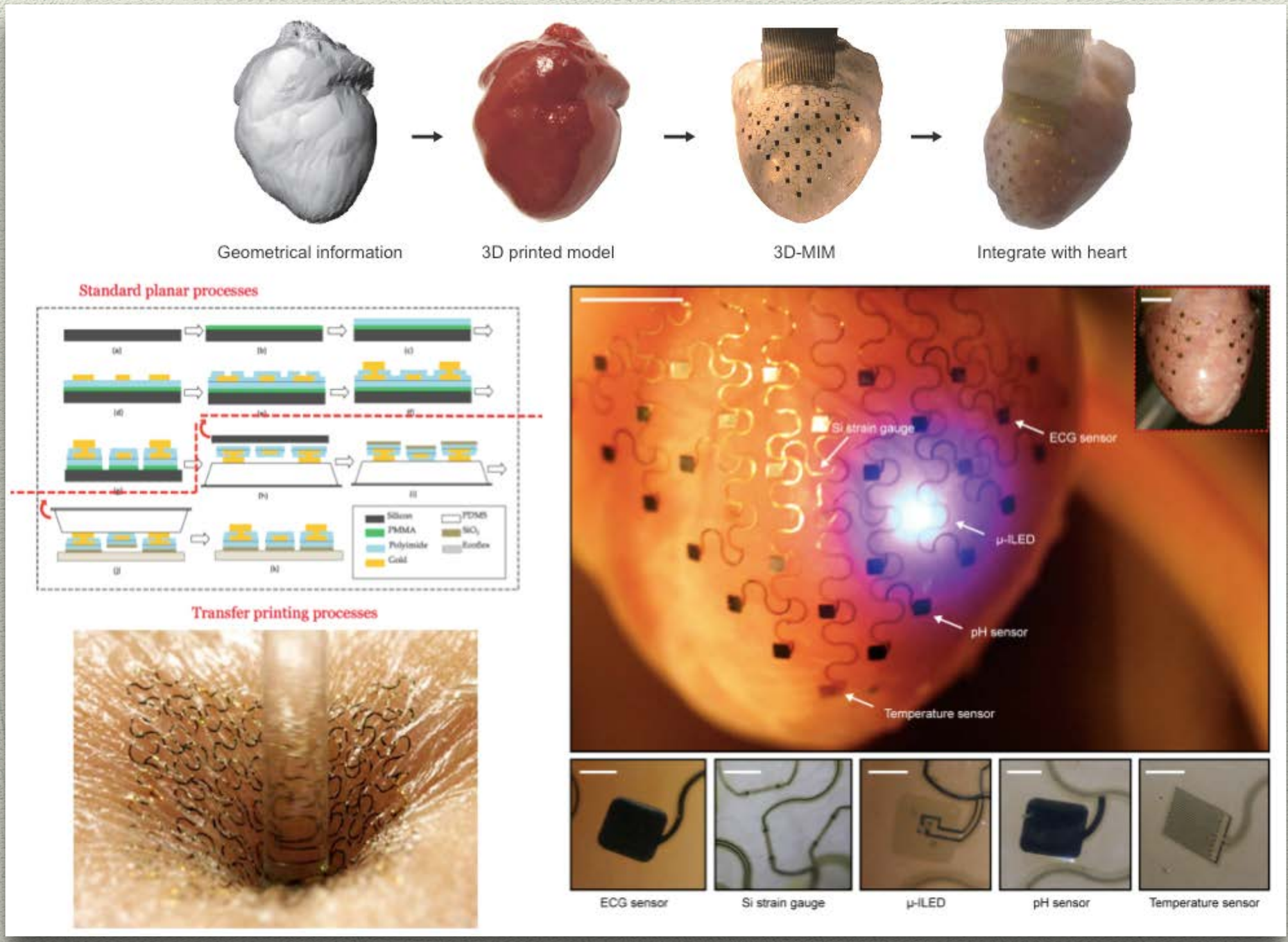
A NEW PARADIGM FOR VT ABLATION

CardioSolv™ is an early stage company developing new strategies to improve the treatment of patients with Ventricular Tachycardia (VT), a life-threatening arrhythmia.

FIND OUT MORE

Contact
contact@cardiosolv.com

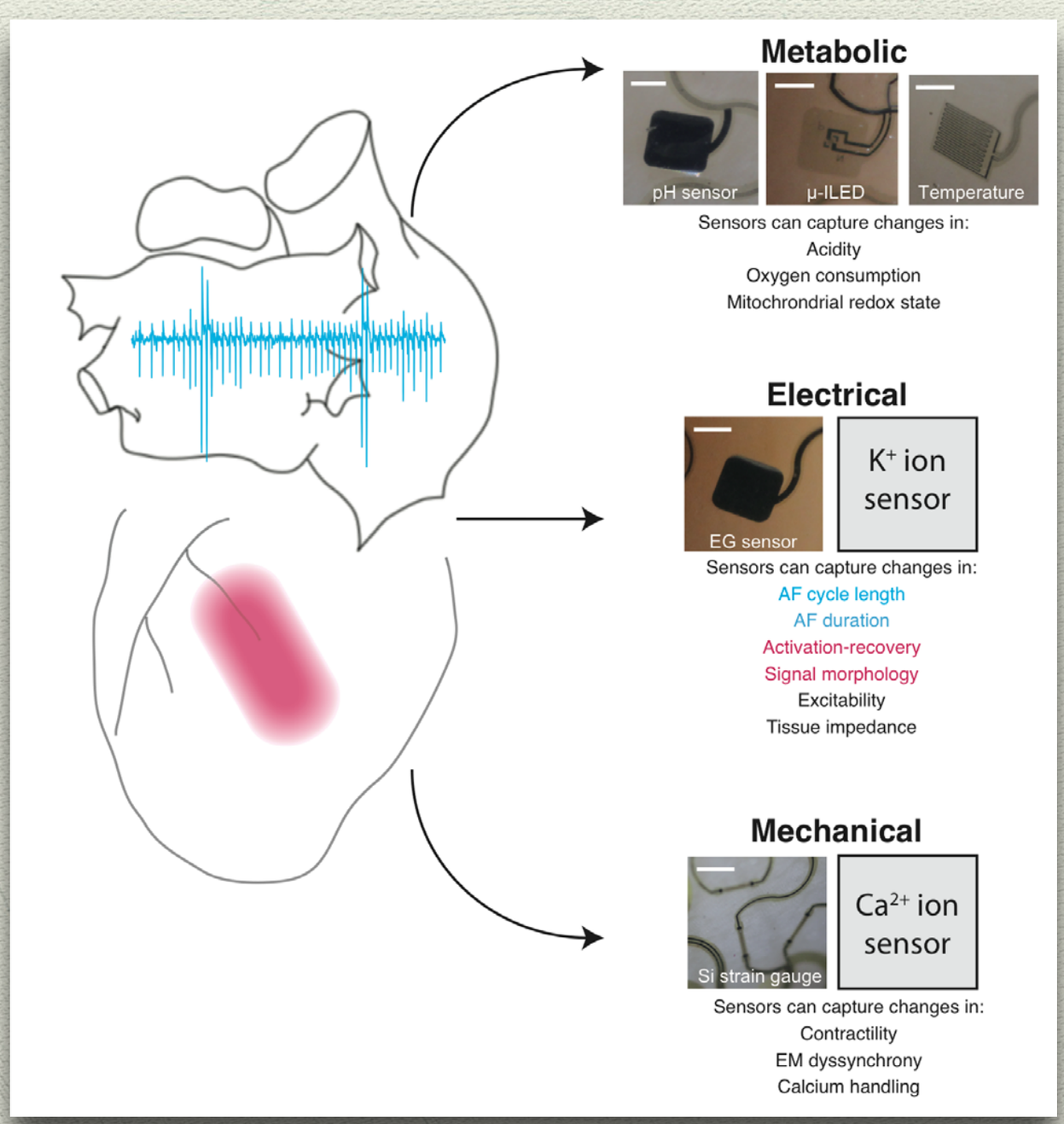
3D Multifunctional Integumentary Membranes (3D-MIMs) for high-density cardiac mapping and stimulation



Xu et al, Nature Communication, 2014

Patient-specific Multifunction High-definition Diagnostics and Therapy

- **Medical imaging provides high-resolution organ anatomy as an input for 3D printing of device manufacturing**
- **Stretchable/flexible electronics platform offers numerous sensors and actuators for high definition diagnostics and therapy**
- **Energy harvesting offers the power**
- **Transient electronics technology offers biodegradable device approach**
- **New devices will address metabolic, electrical and mechanical dysfunction**



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