Autonomic Regulation of Cardiac Excitability: Technology Response

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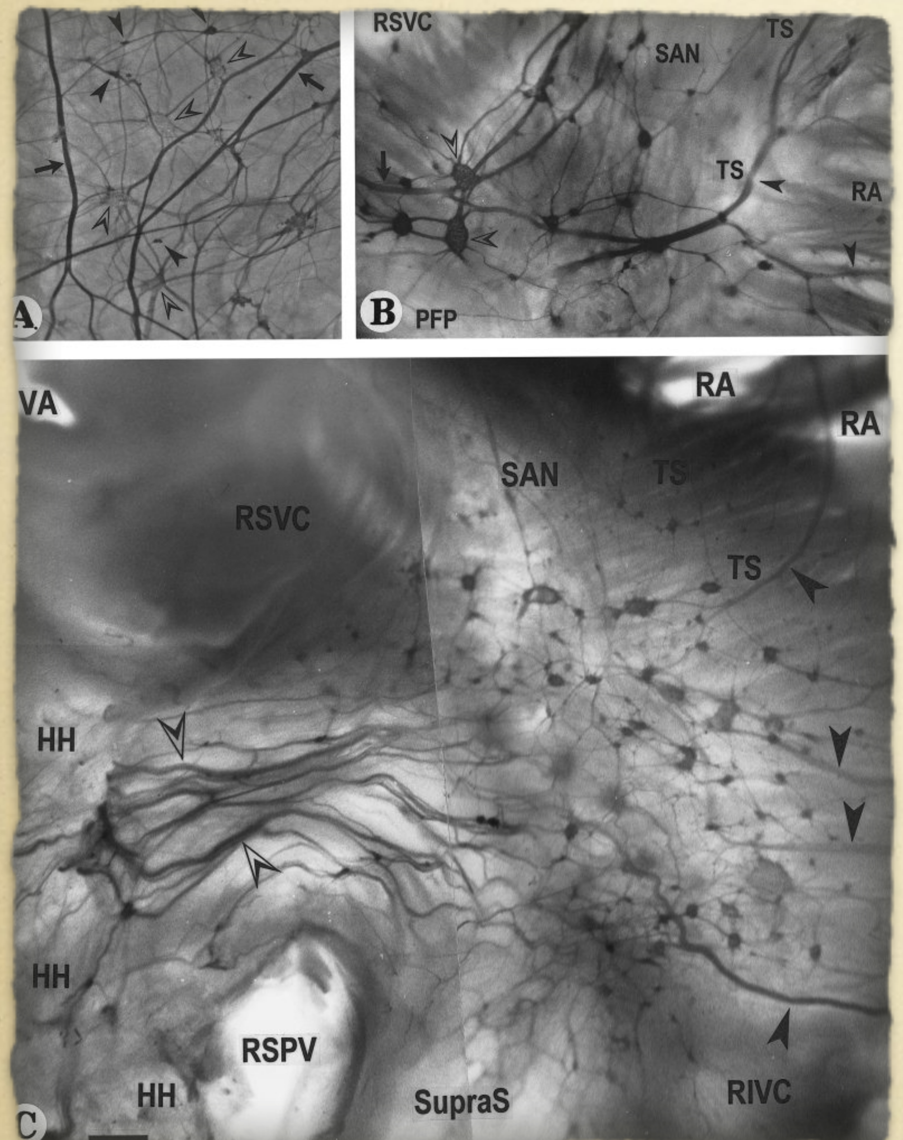
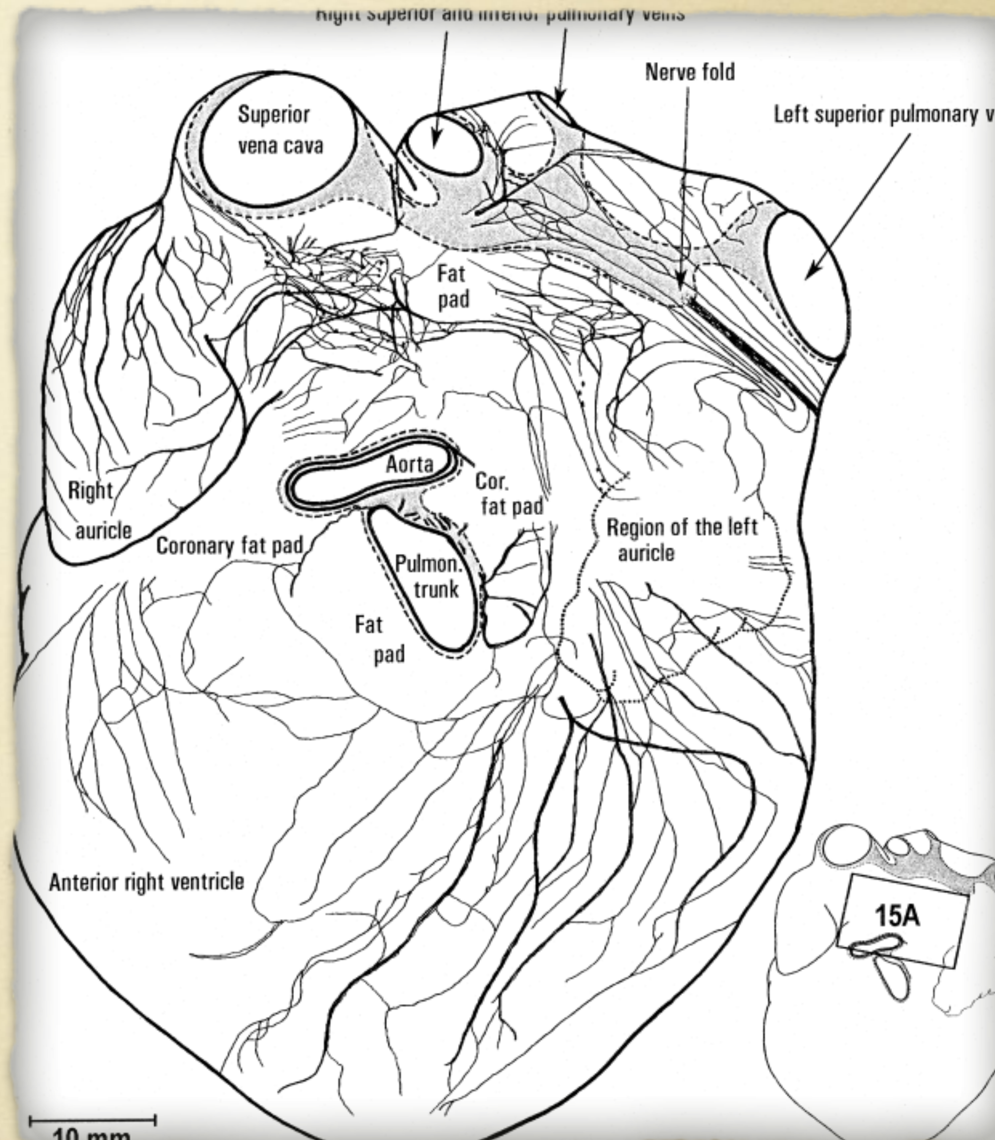
Challenges

- Multiple anatomical scales
- Mapping autonomic and cardiac function
- From mouse to man: lost in translation
- New instrumentation

"Little brain" of the human heart

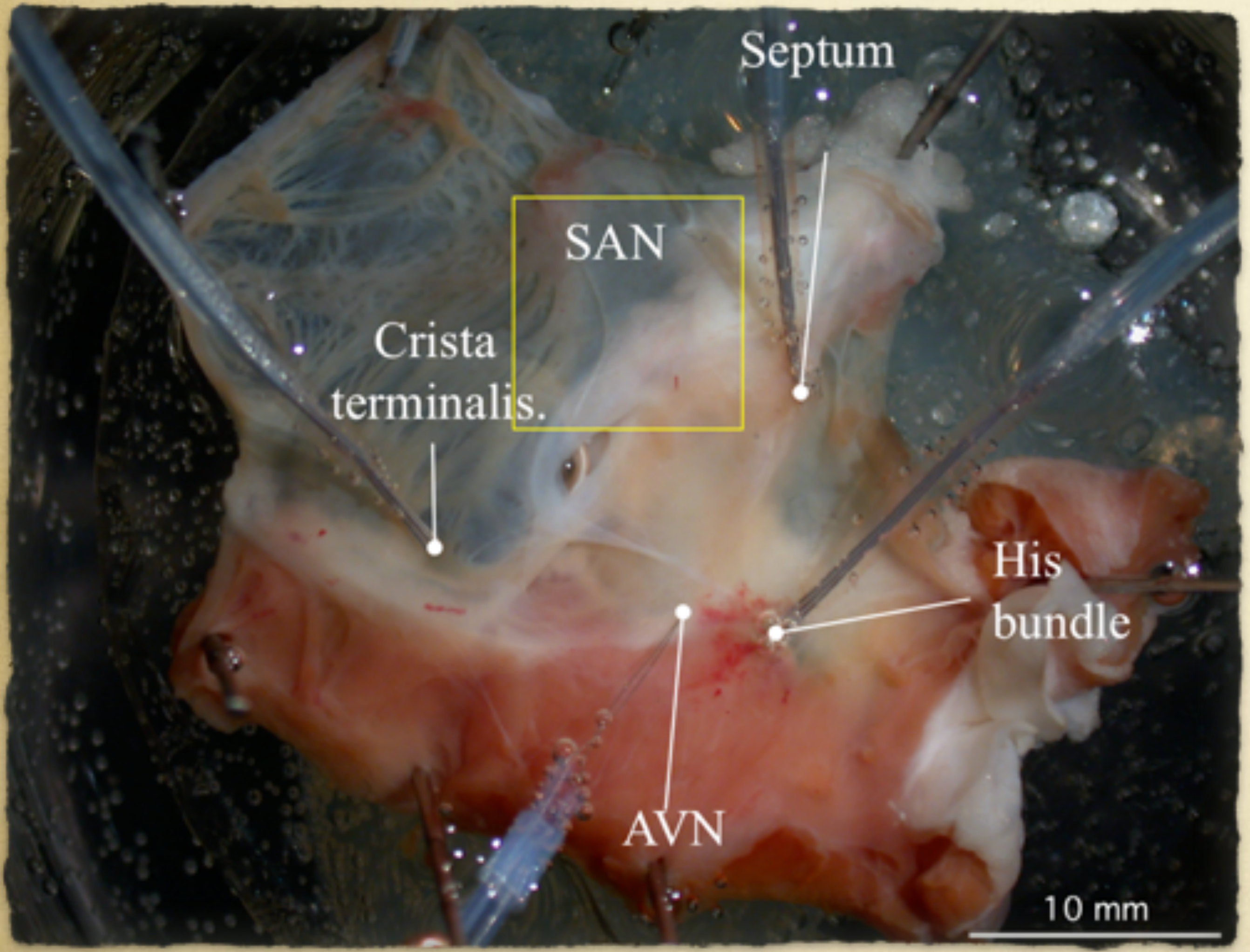


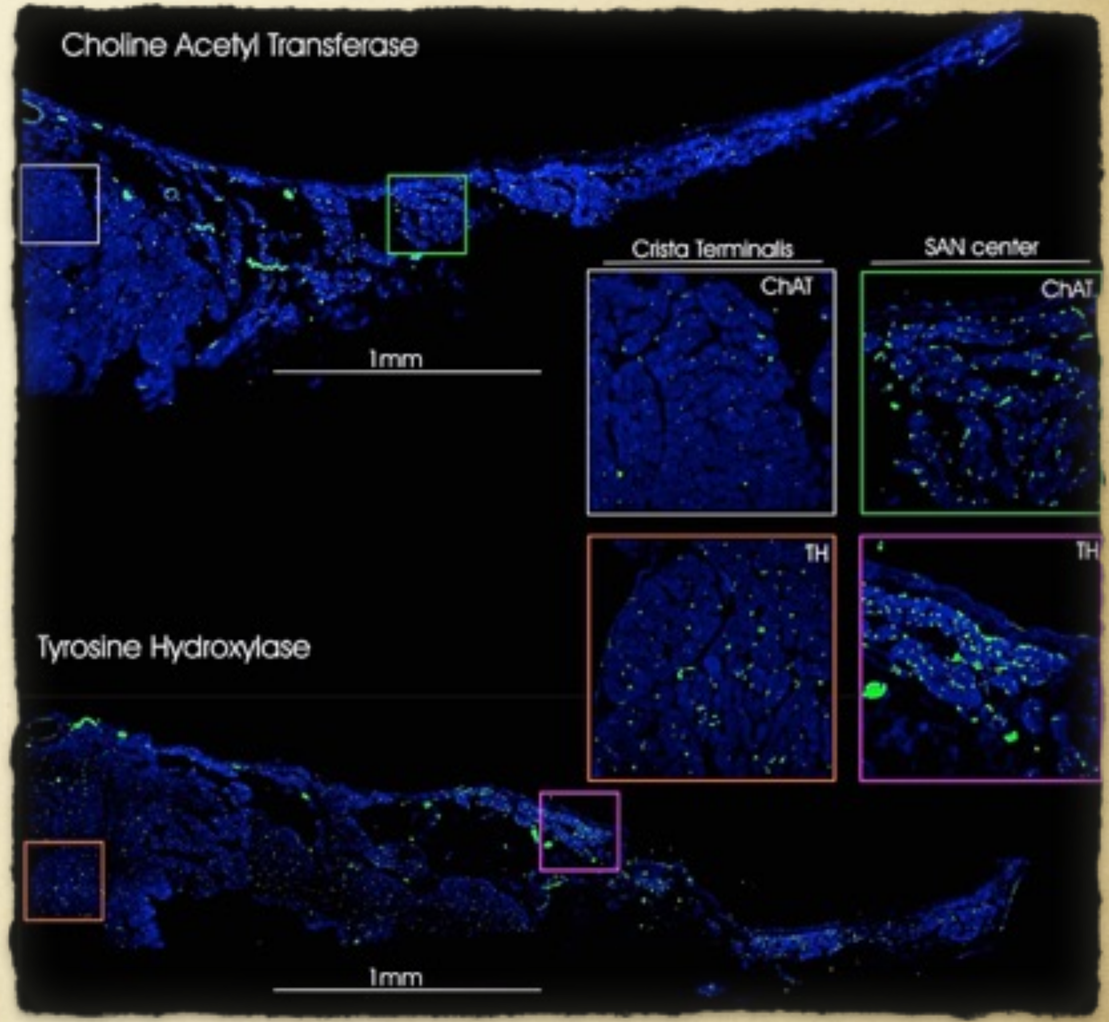
Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses. Pauza et al. Anat. Rec. 2000



Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses. Pauza et al. Anat. Rec. 2000

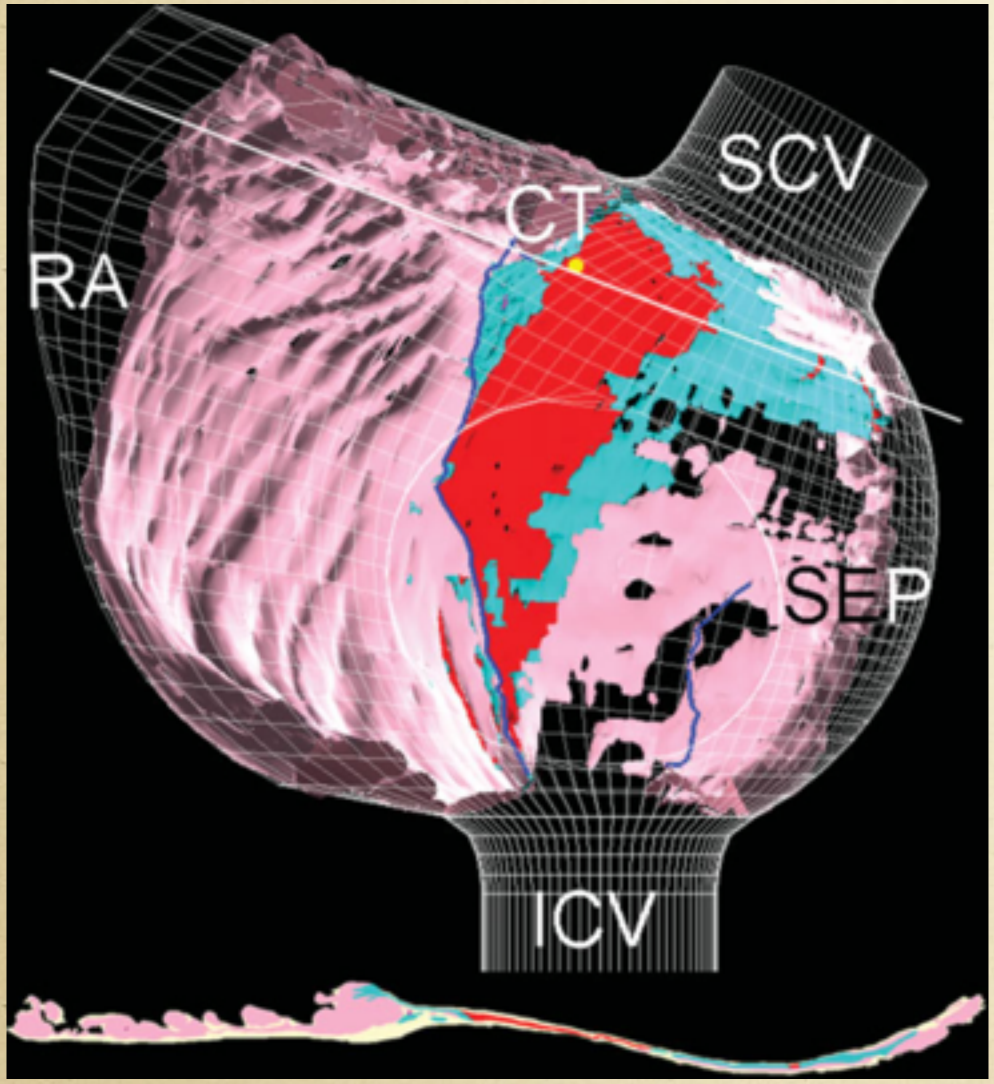
SA Node: Molecular Mapping



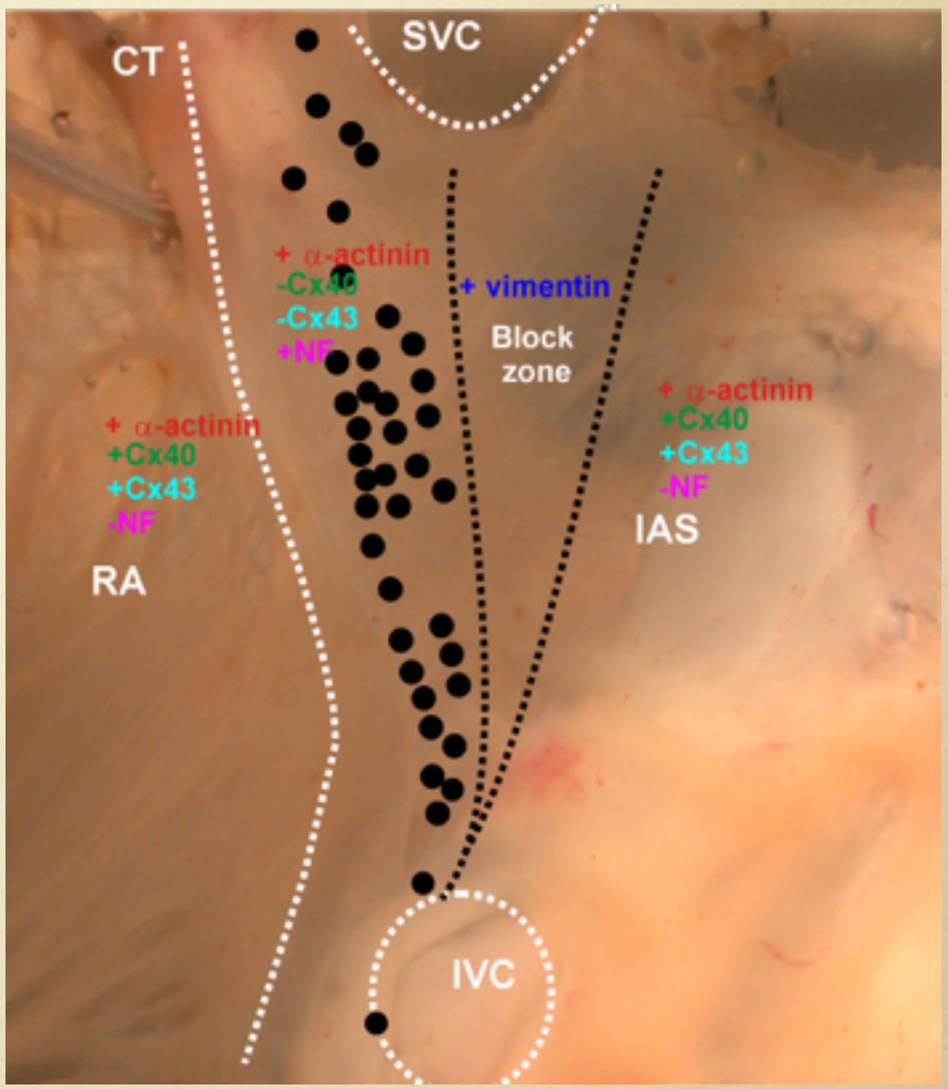


Fedorov, AJP: Heart. 2006

SAN Structure/Function

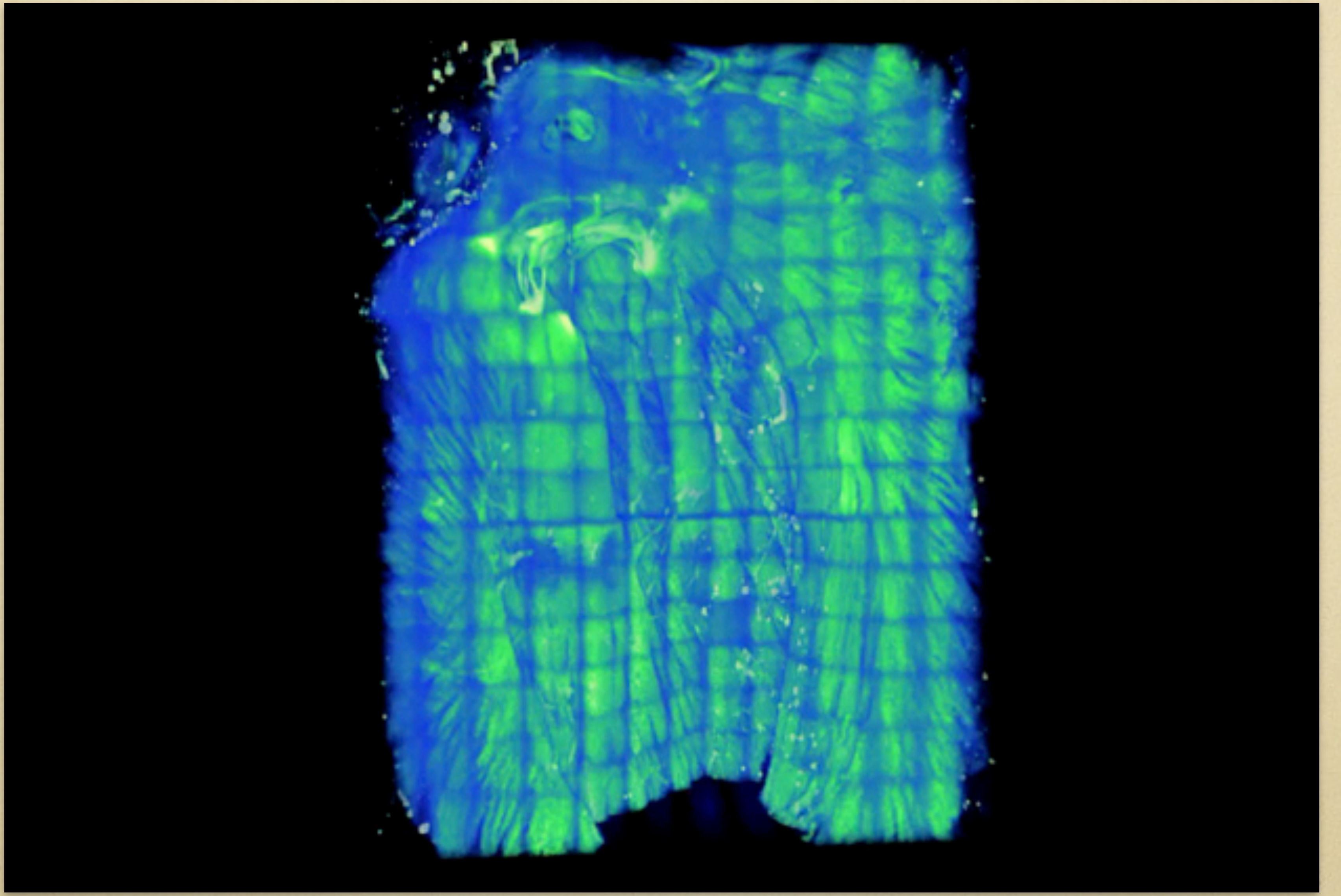


Dobrzynski, 2005.



Fedorov, 2006

Cardiac C.L.A.R.I.T.Y.



Light sheet microscopy of cleared mouse left ventricle: blue- DAPI, green- Cx43
Holzem, Tomer, et al, unpublished 2015

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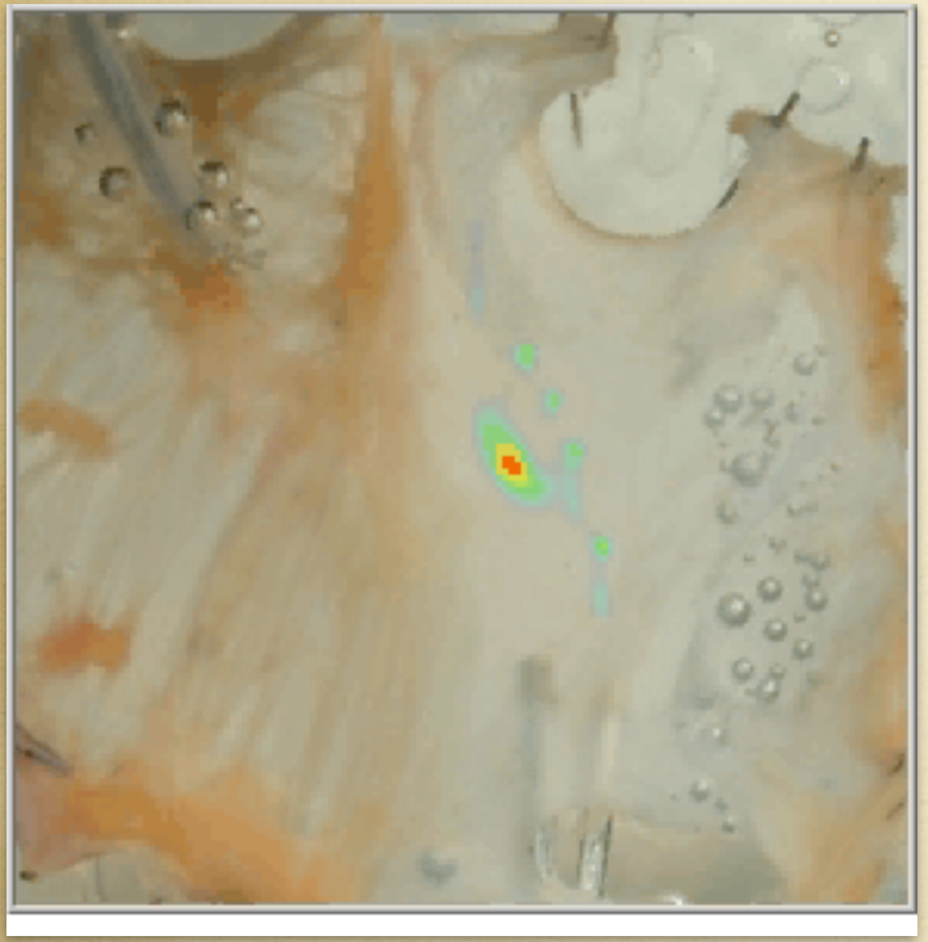
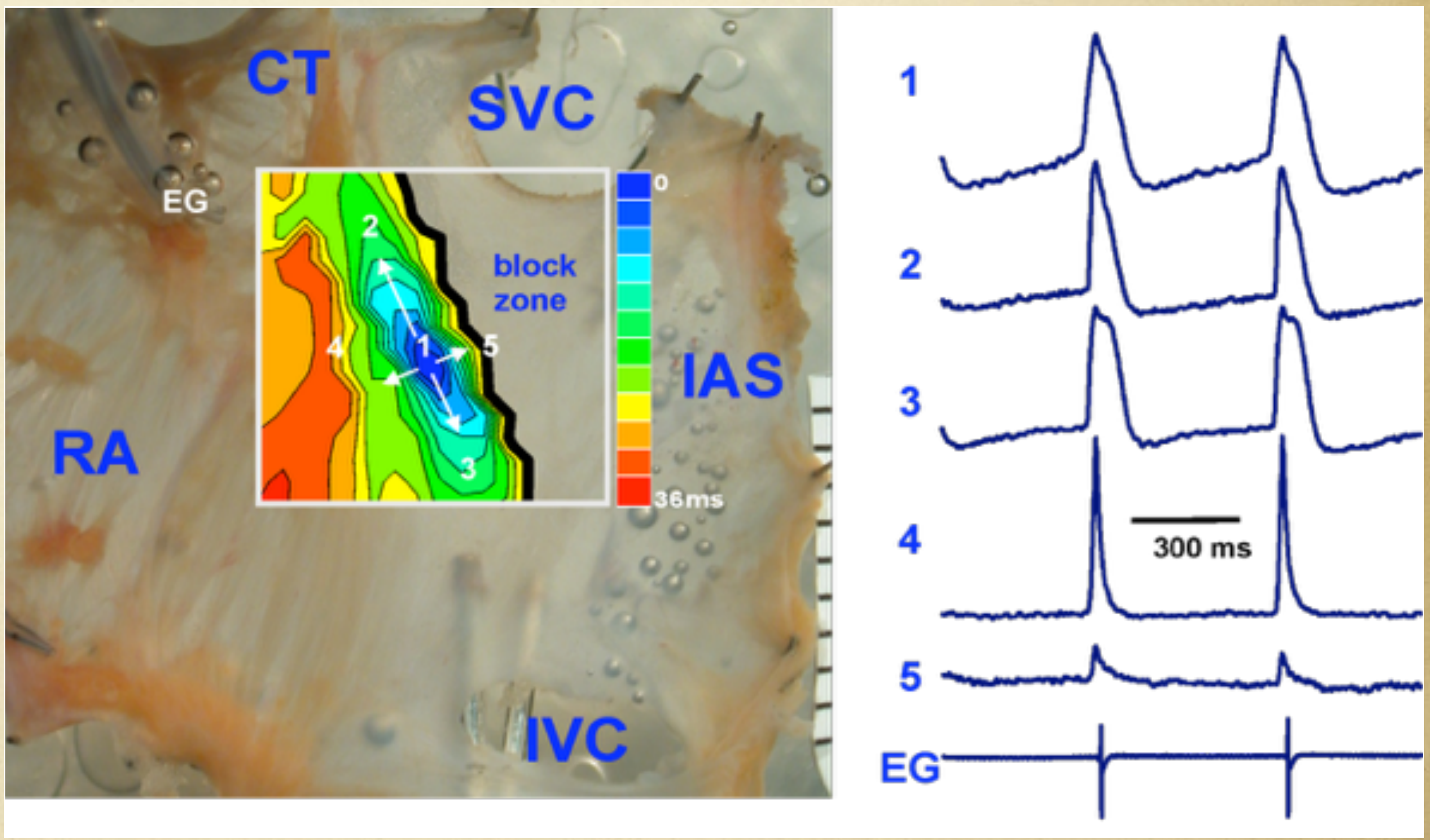
SA Node: Functional Mapping

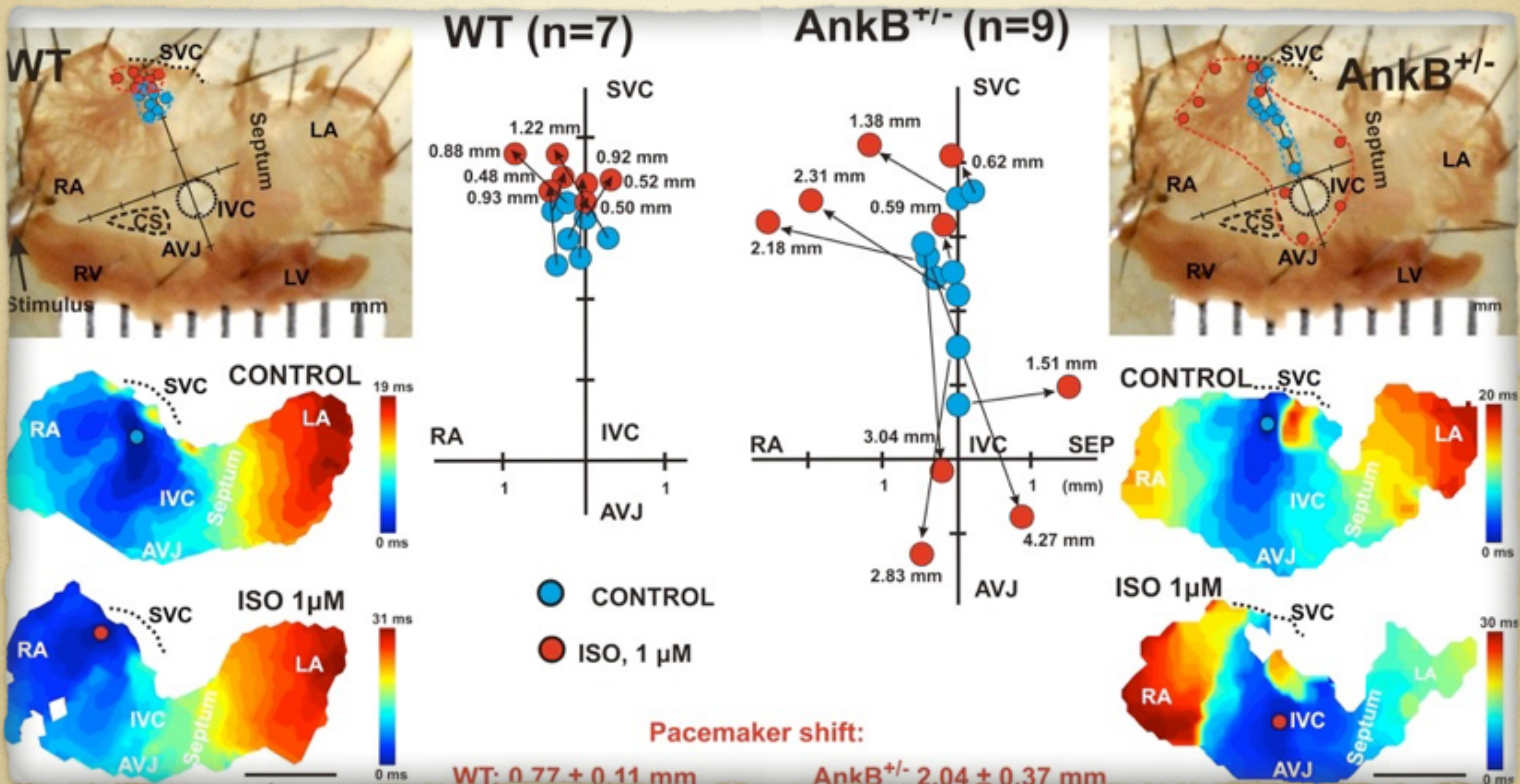




Fedorov, AJP: Heart. 2006

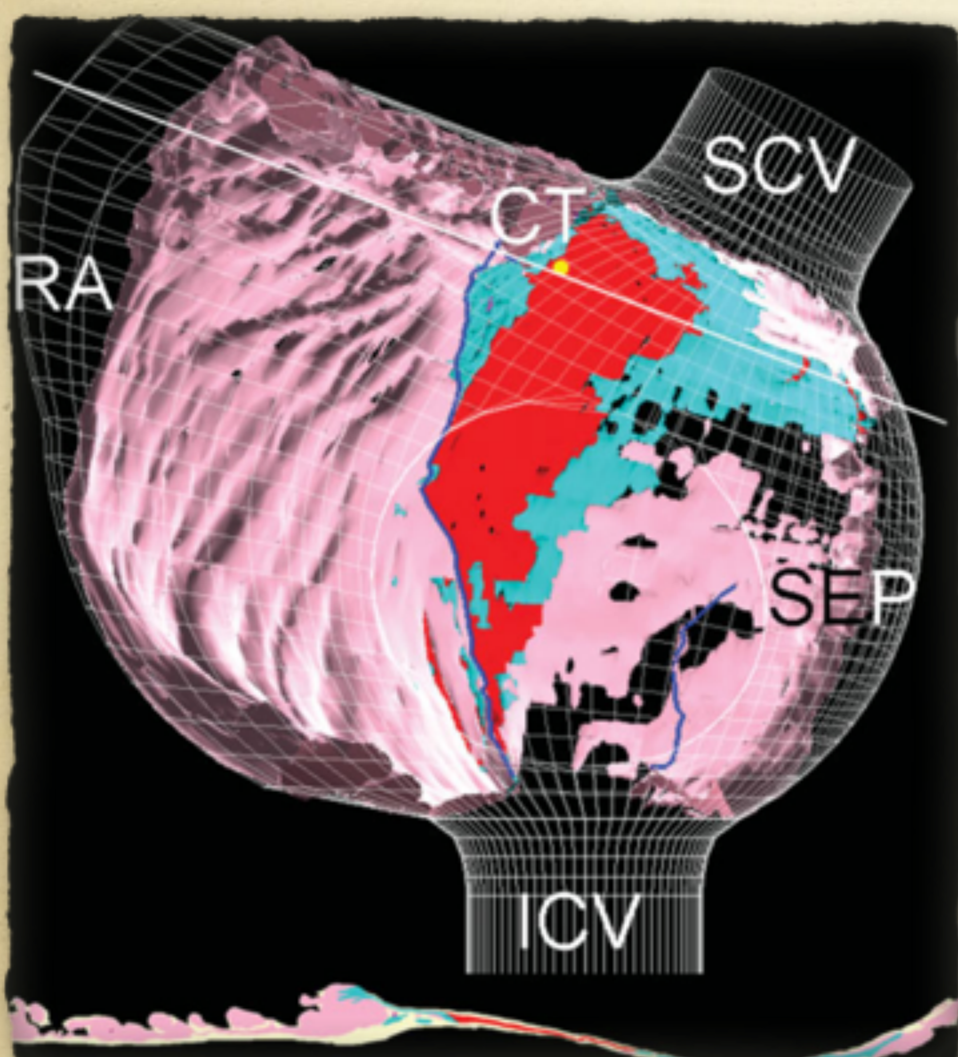
CT- crista terminalis, RA- right atrium, SVC & IVC-superior and inferior vena cava, IAS- interatrial septum

Shift of mouse pacemaker during sympathetic (ISO) stimulation

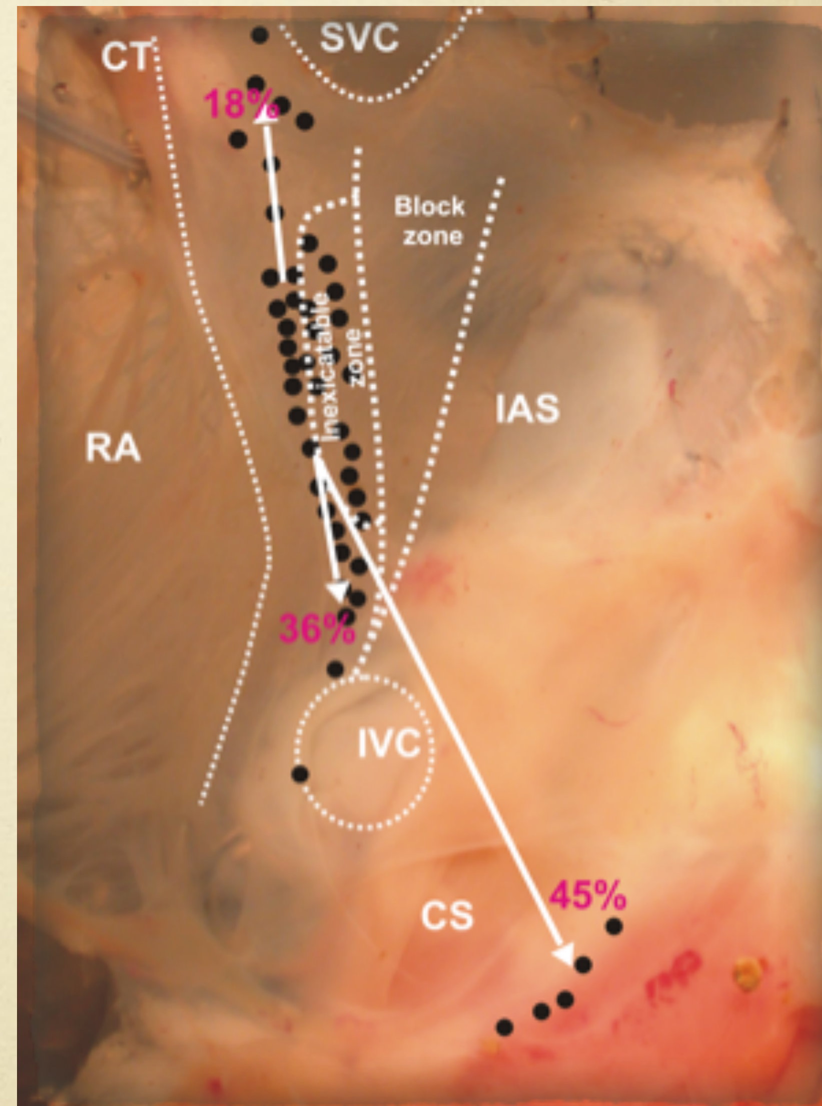


Glukhov, AJP: Heart. 2010

Shift of pacemaker during vagal stimulation (rabbit)



Distributed pacemaker complex. Dobrzynski, 2005.



Shift of pacemaker during vagal stimulation. Fedorov, 2006

★ EDITOR'S CHOICE ★

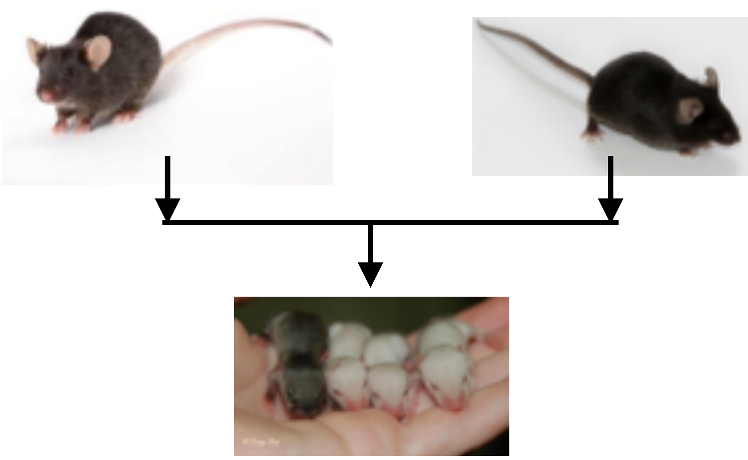
Optogenetic release of norepinephrine from cardiac sympathetic neurons alters mechanical and electrical function

Anastasia M. Wengrowski, Xin Wang, Srinivas Tapa, Nikki Gillum Posnack, David Mendelowitz, Matthew W. Kay

DOI: http://dx.doi.org/10.1093/cvr/cvu258 143-150 First published online: 16 December 2014

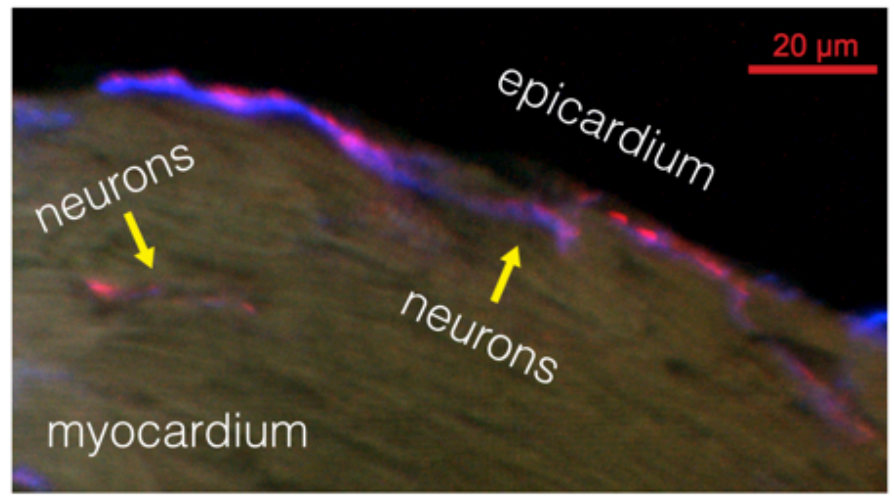
Tyrosine hydroxylase promoter of Cre expression

ChR2 expression dependent upon Cre expression

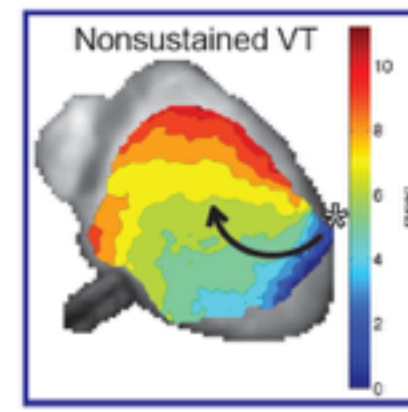


Offspring express ChR2 in cells having tyrosine hydroxylase (NE/E producing neurons).

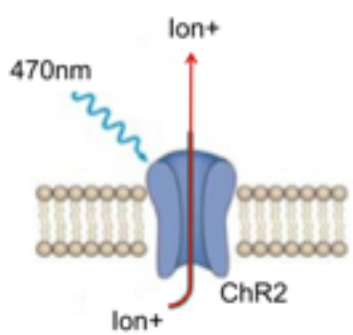
Cardiac sympathetic nerve fibers selectively express EYFP/ ChR2. Blue: EYFP/ChR2, Red: tyrosine hydroxylase.

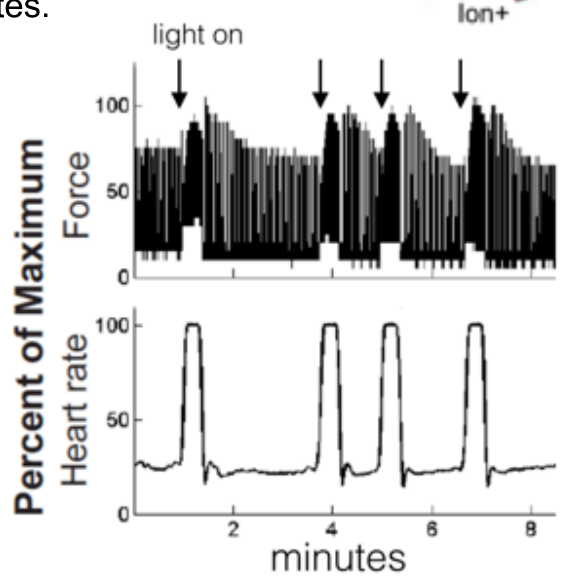


Increased incidence of arrhythmia was observed immediately after optical activation of sympathetic nerve fibers.



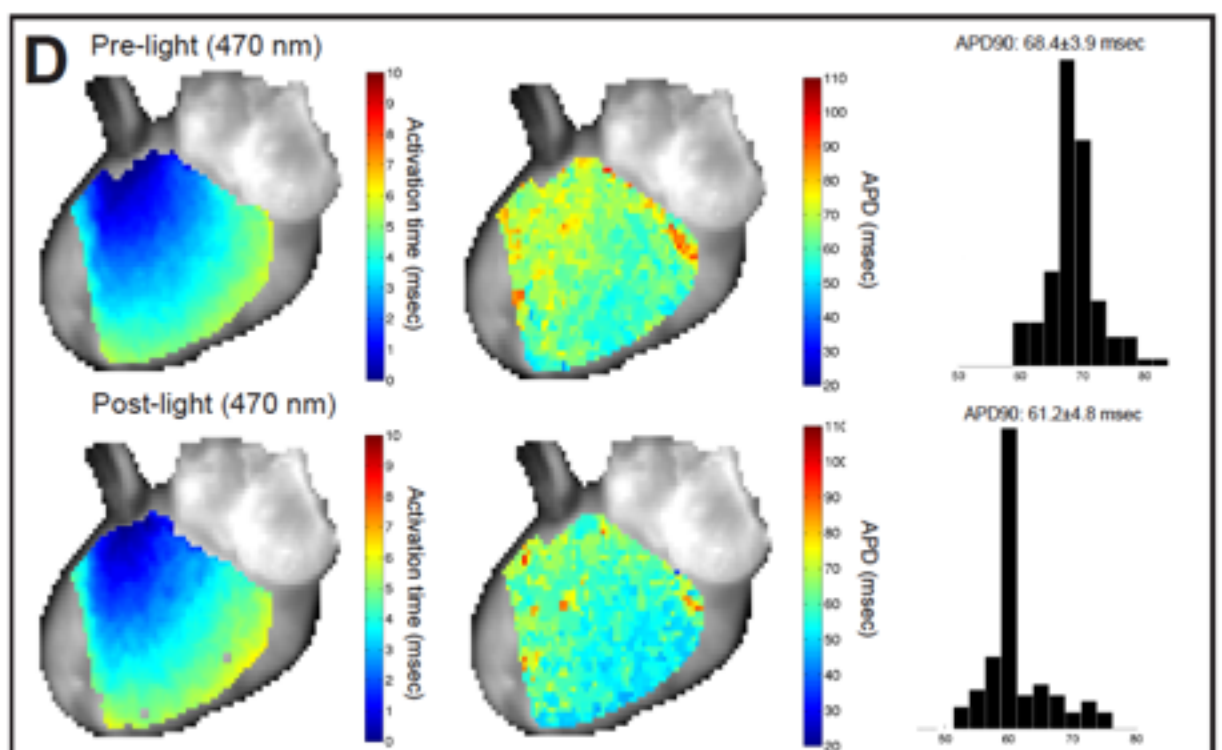
Energize ChR2 with blue light to depolarize sympathetic nerve cardiac axons. The release of NE activates beta-adrenergic pathways in cardiac myocytes.

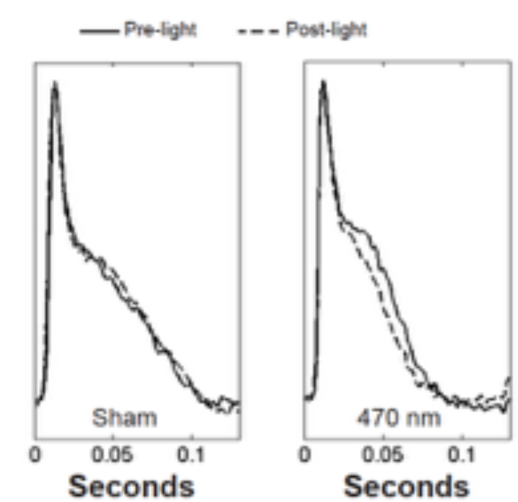




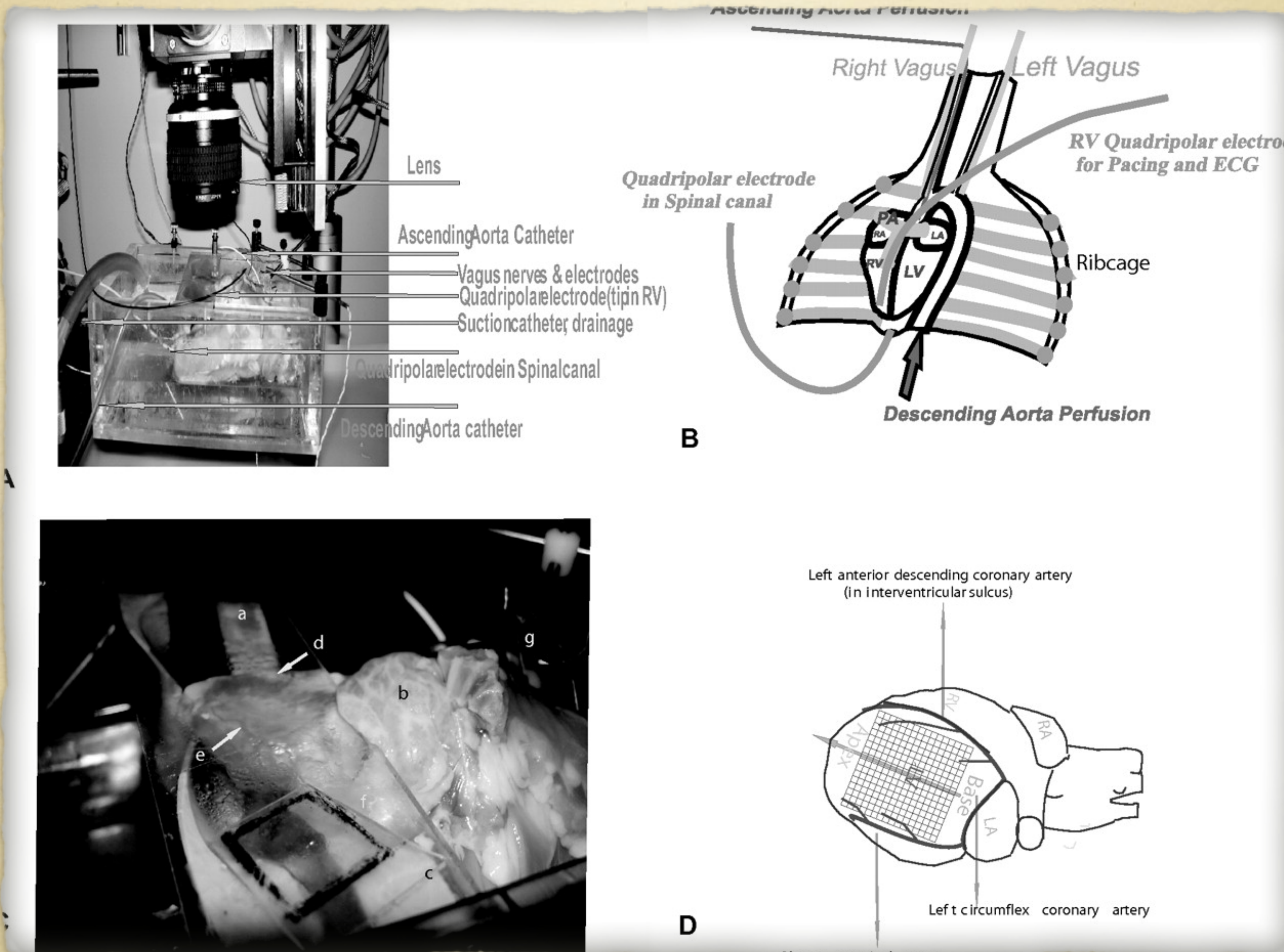
Optical activation of sympathetic nerve fibers increased HR and contractile force.

Optical mapping of epicardial membrane potential immediately after optical activation of sympathetic nerve fibers reveals reduced APD.





Isolated innervated heart preparation



Mantravadi. Circ Res. 2007

Challenges

- Multiple anatomical scales
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Transgenic Mouse "Wet Bench" Legacy

- "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, <u>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.</u> 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."
- Jeffrey Robbins, "Twenty Years of Gene Targeting: What We Don't Know?", Circulation Research, 2011, 109:722-723.

Mid-America Transplant Services in St. Louis

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]

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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
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require
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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
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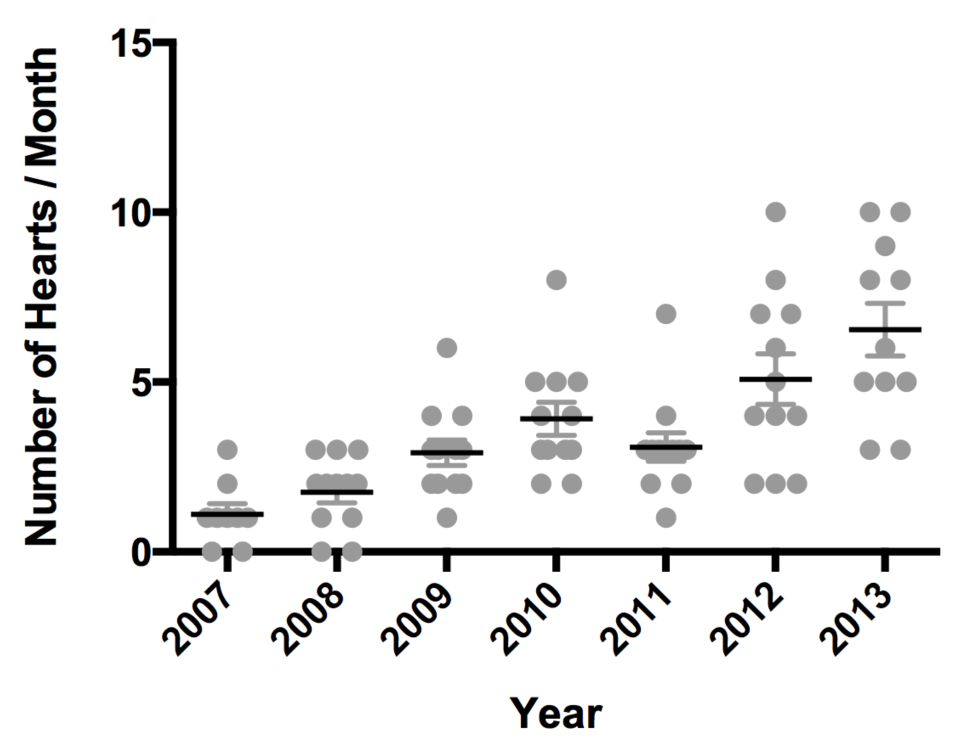
[5]Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC

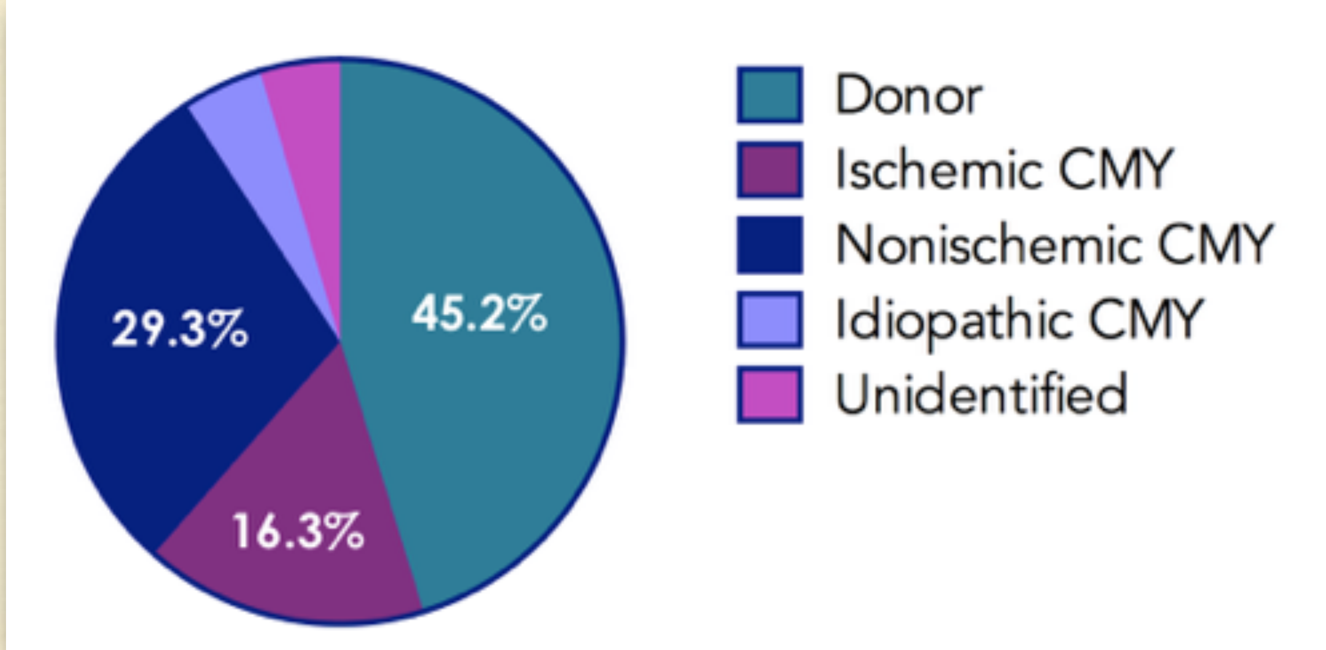
criteria for donor heart evaluation and acceptance for transplantation.

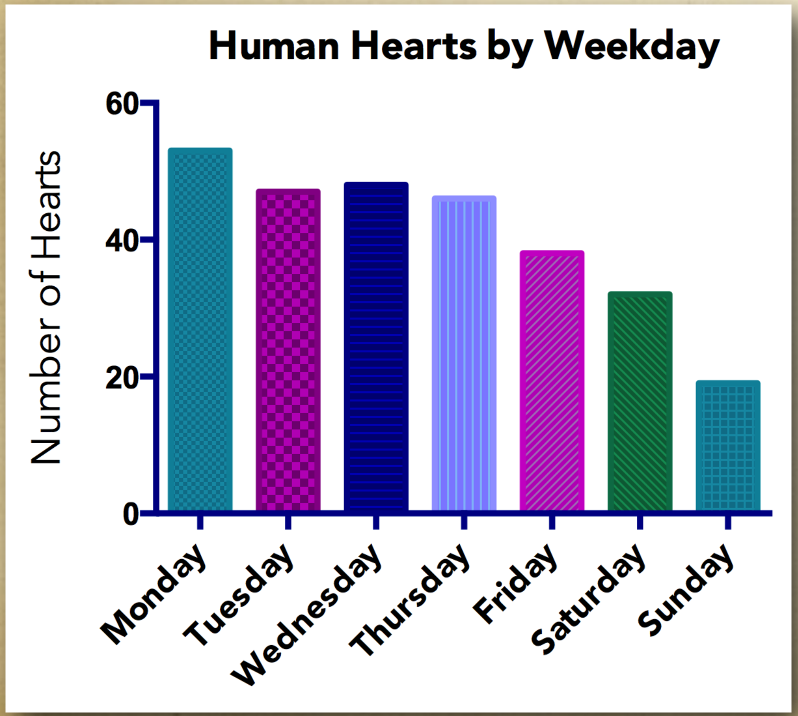
Abbreviations: INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MPSC, Membership Professional Standards Committee; OE, observed to expected; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing

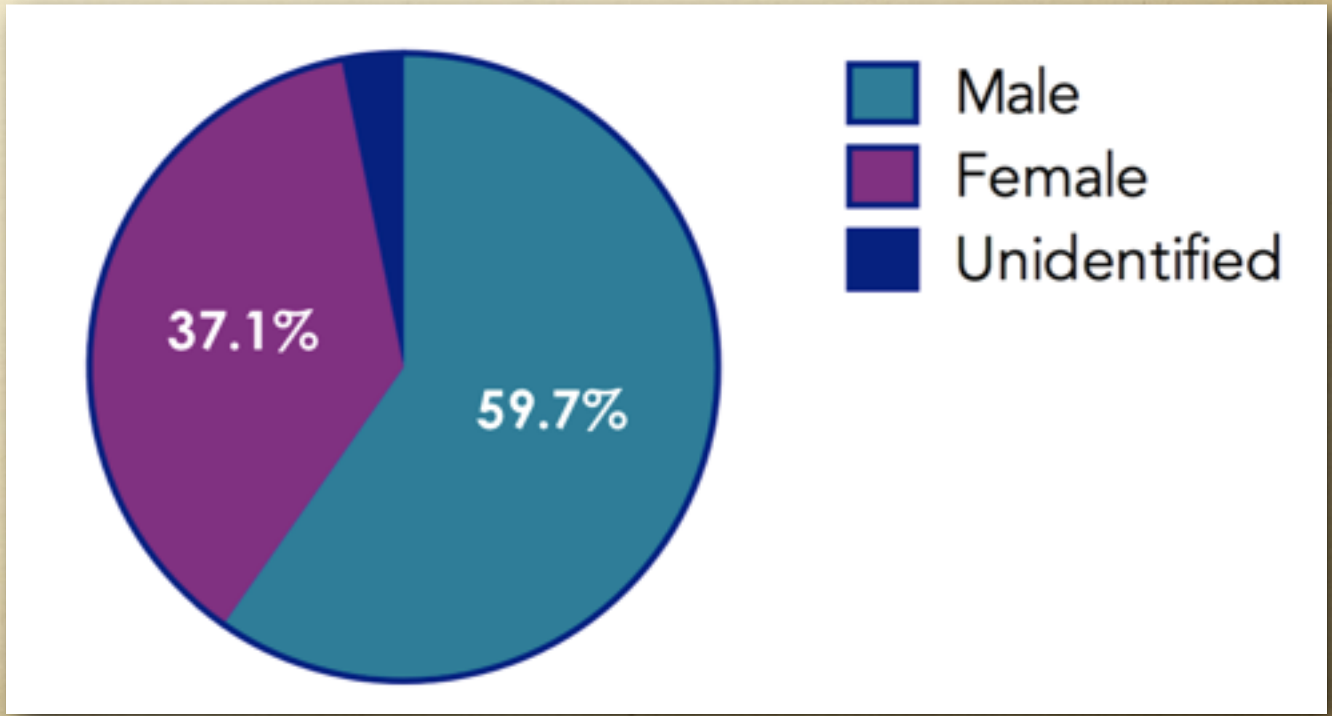
Received 31 August 2014, revised 09 October 2014 and accepted for publication 13 October 2014

The Human Heart Physiology Program
(352 human hearts as of 02/24/15)

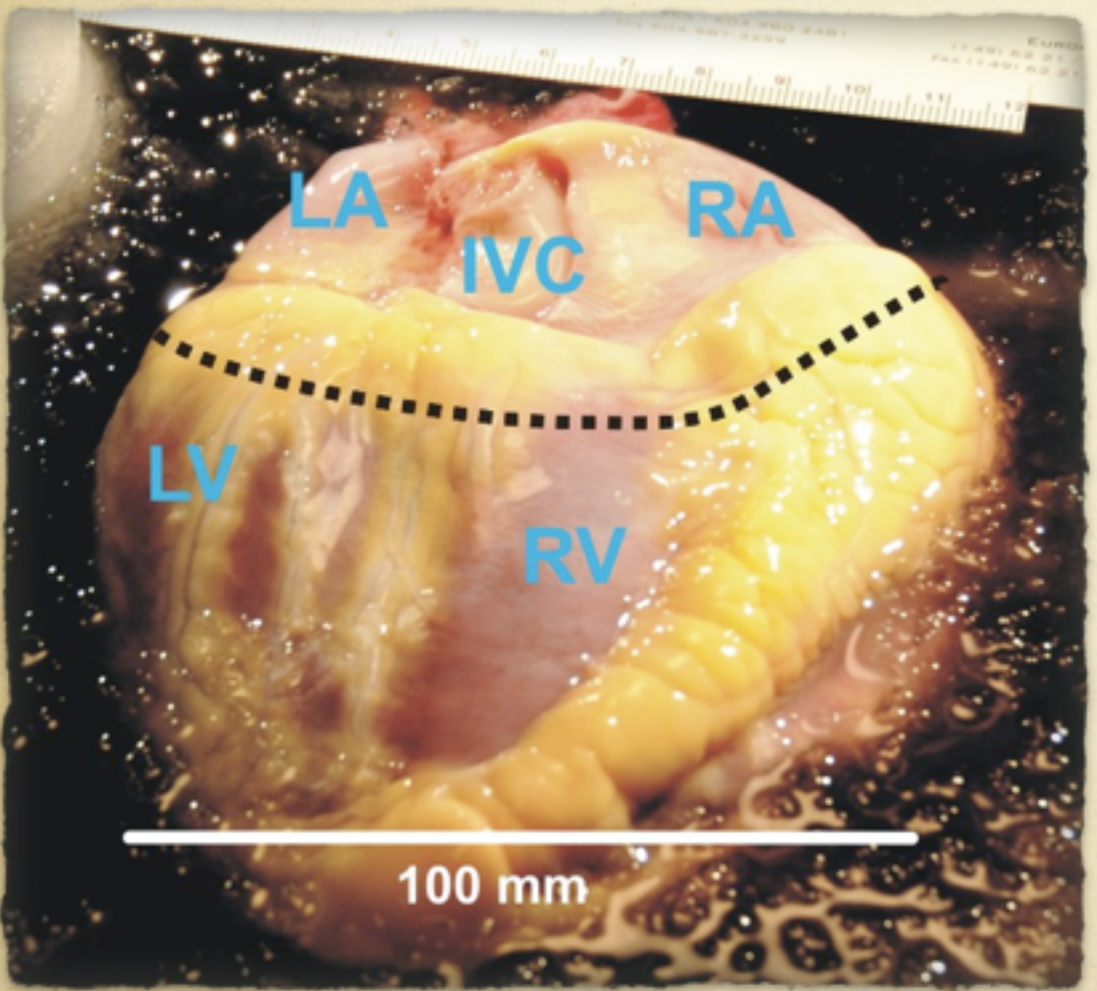


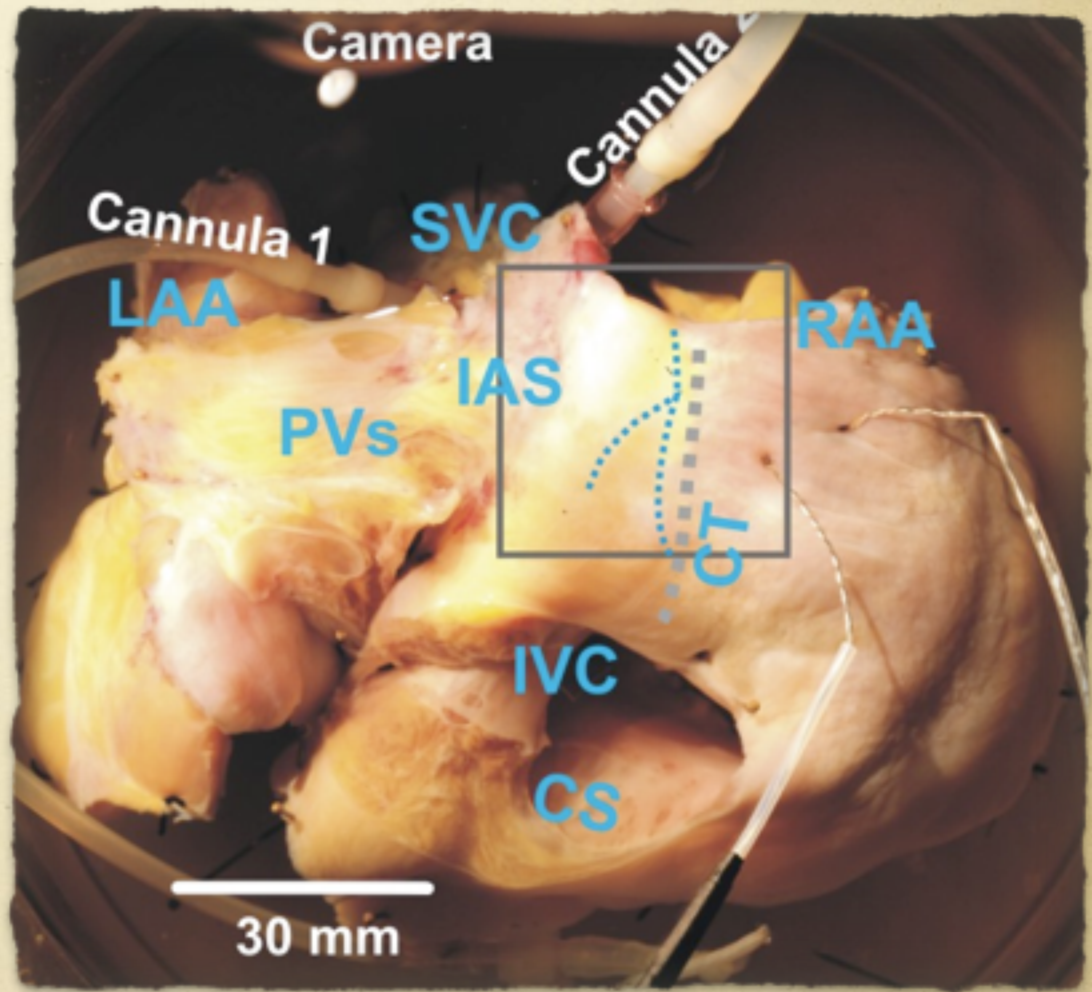






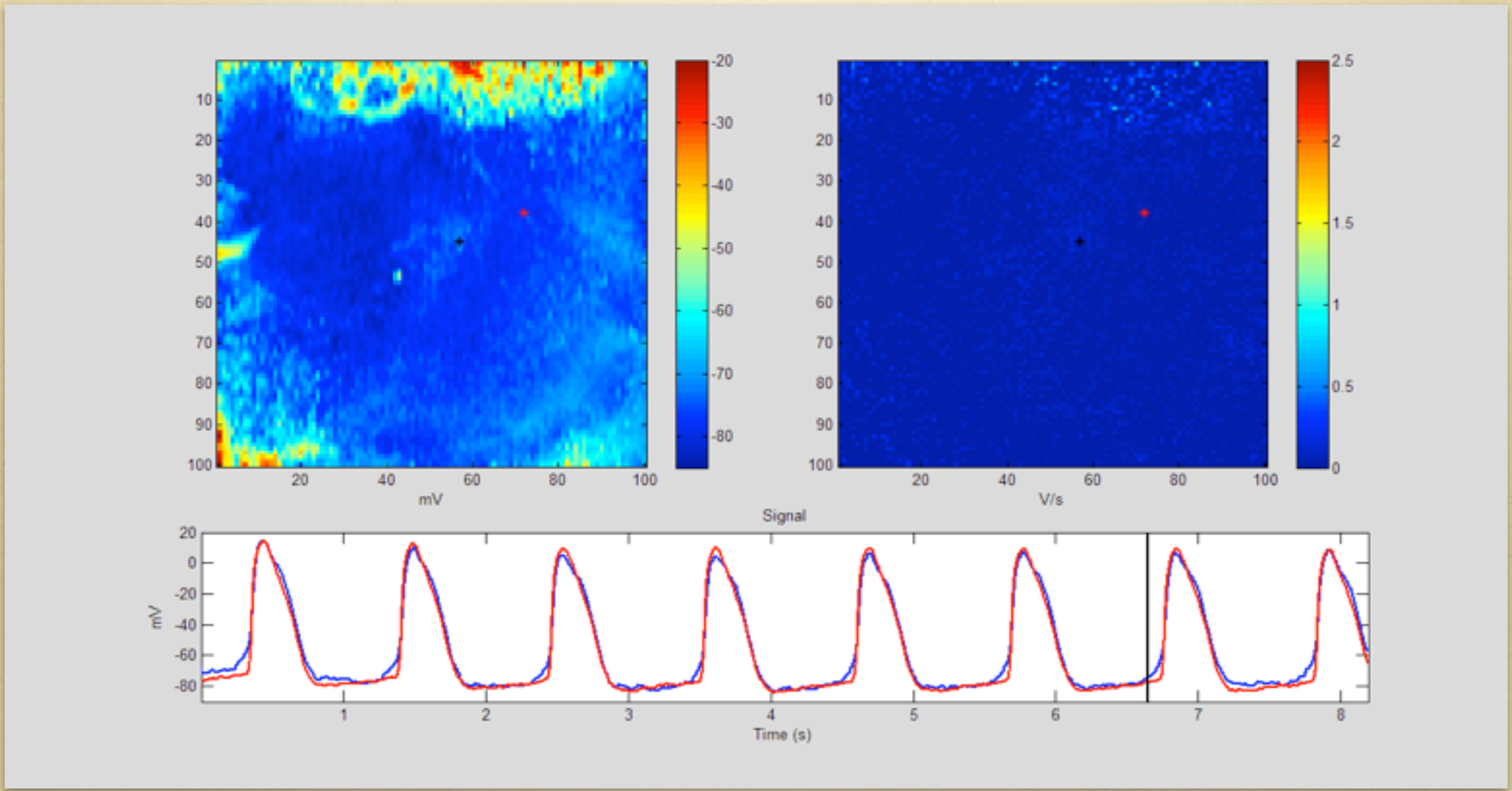
Imaging Human Sinus Node with Voltage-Sensitive Dye Di-4-ANBDQBS





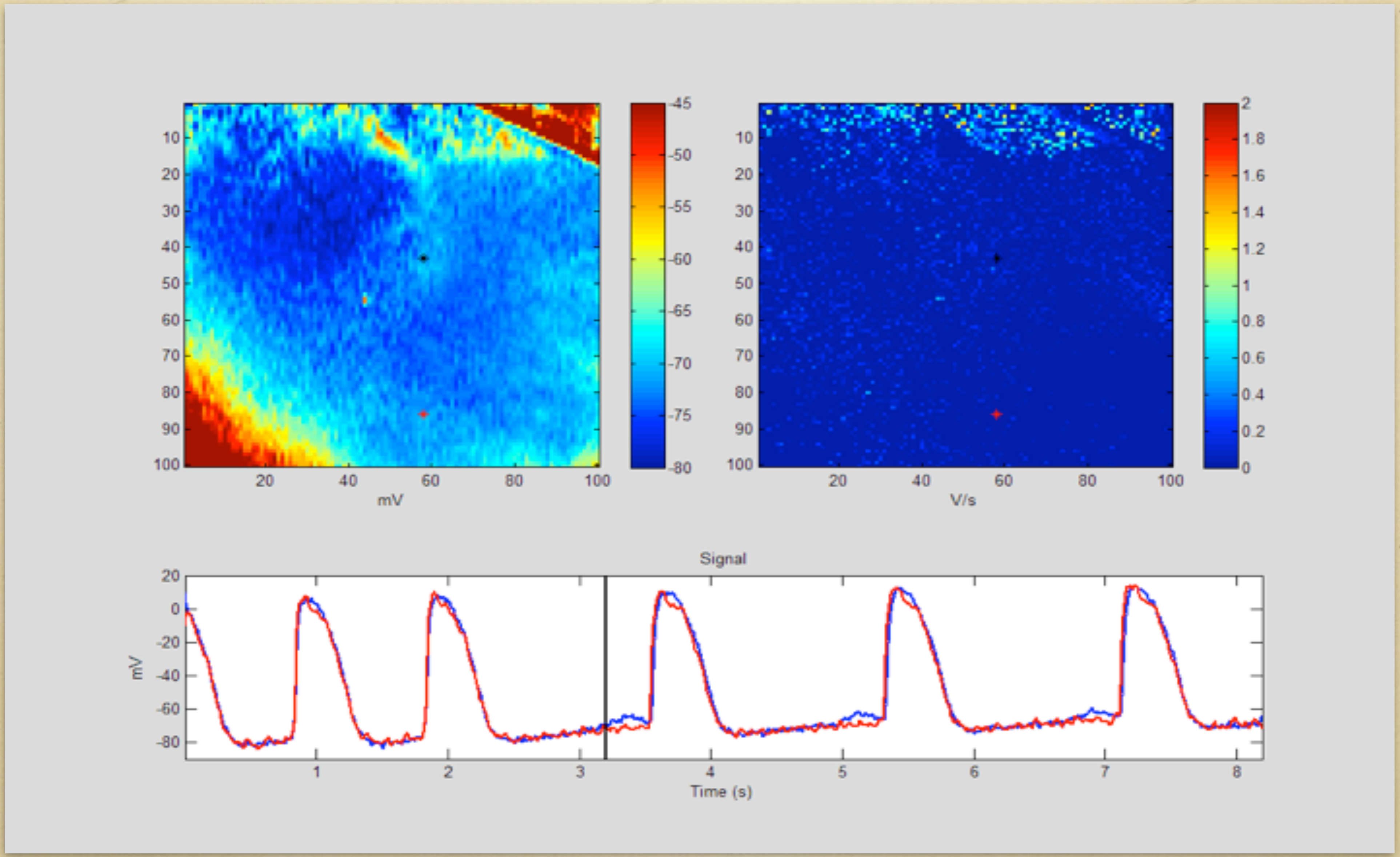
Fedorov, JACC, 2010

Imaging Human Sinus Node: Evidence of the Superior Sino-Atrial Pathway



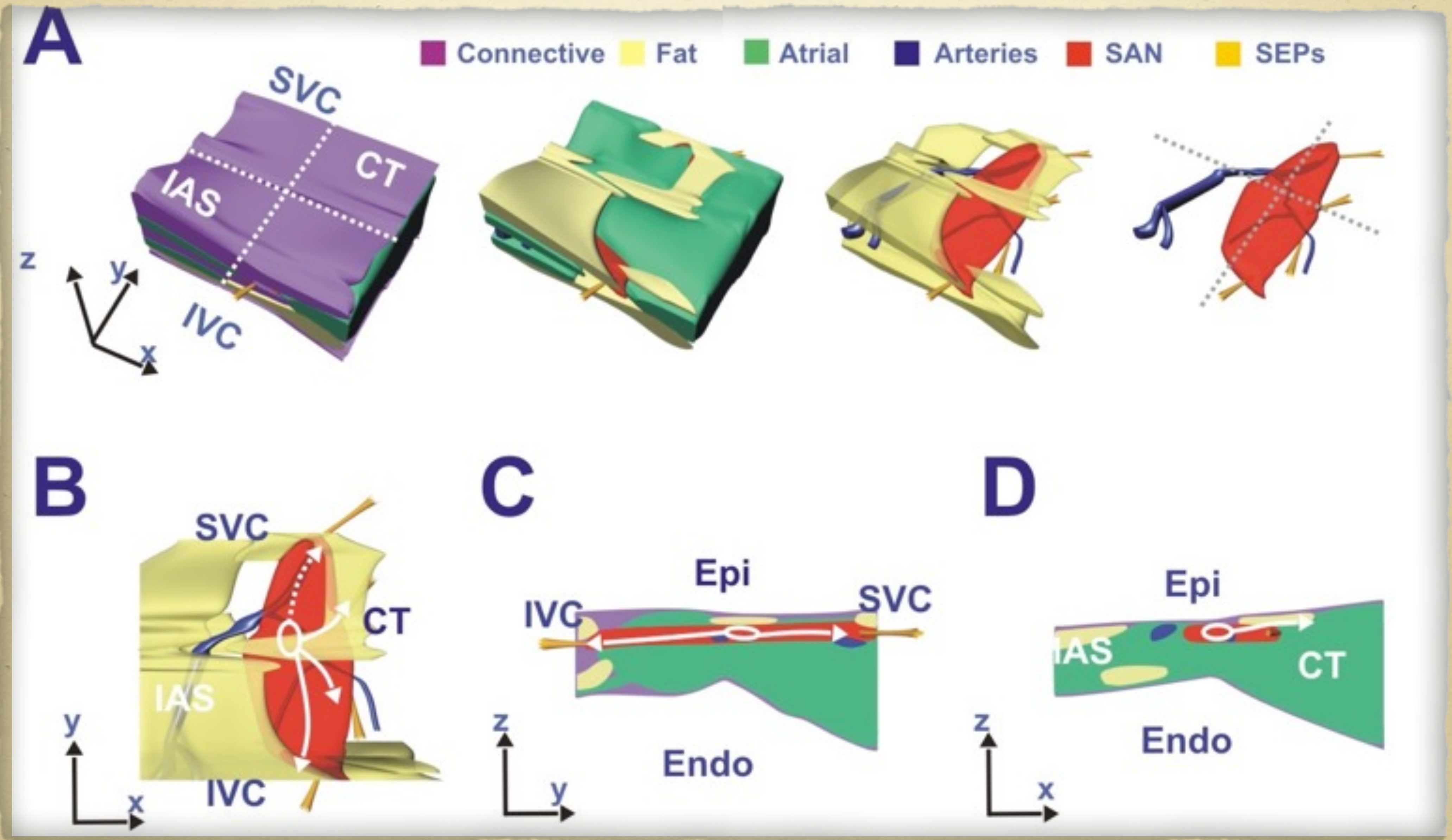
Fedorov, JACC, 2010

Imaging Human Sinus Node: Evidence of the Inferior Sino-Atrial Pathway



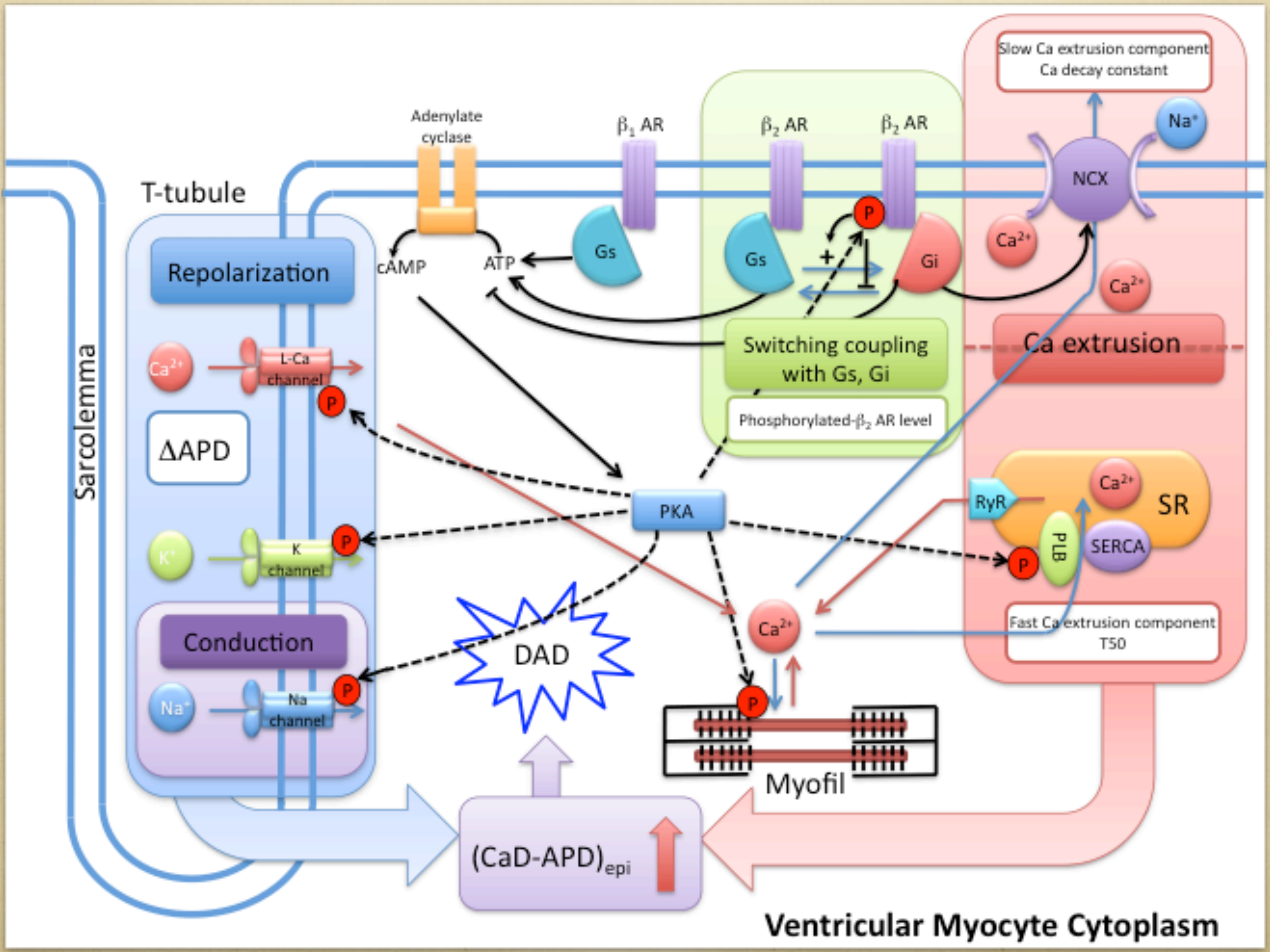
Fedorov, JACC, 2010

3D Structure of the Human Sinus Node and the Exit Pathways

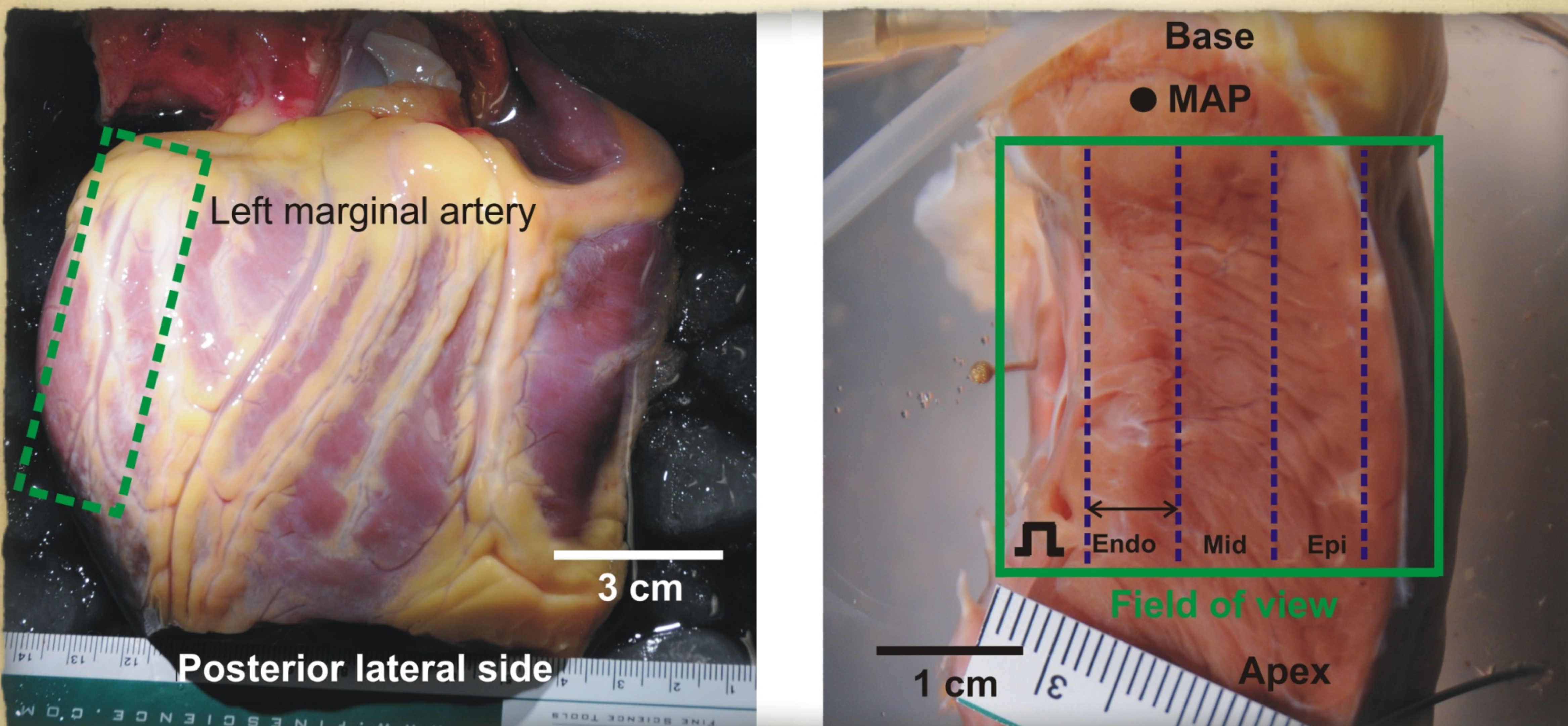


Fedorov, JACC, 2010

β_1 vs. β_2 adrenergic receptor remodeling in human failing heart

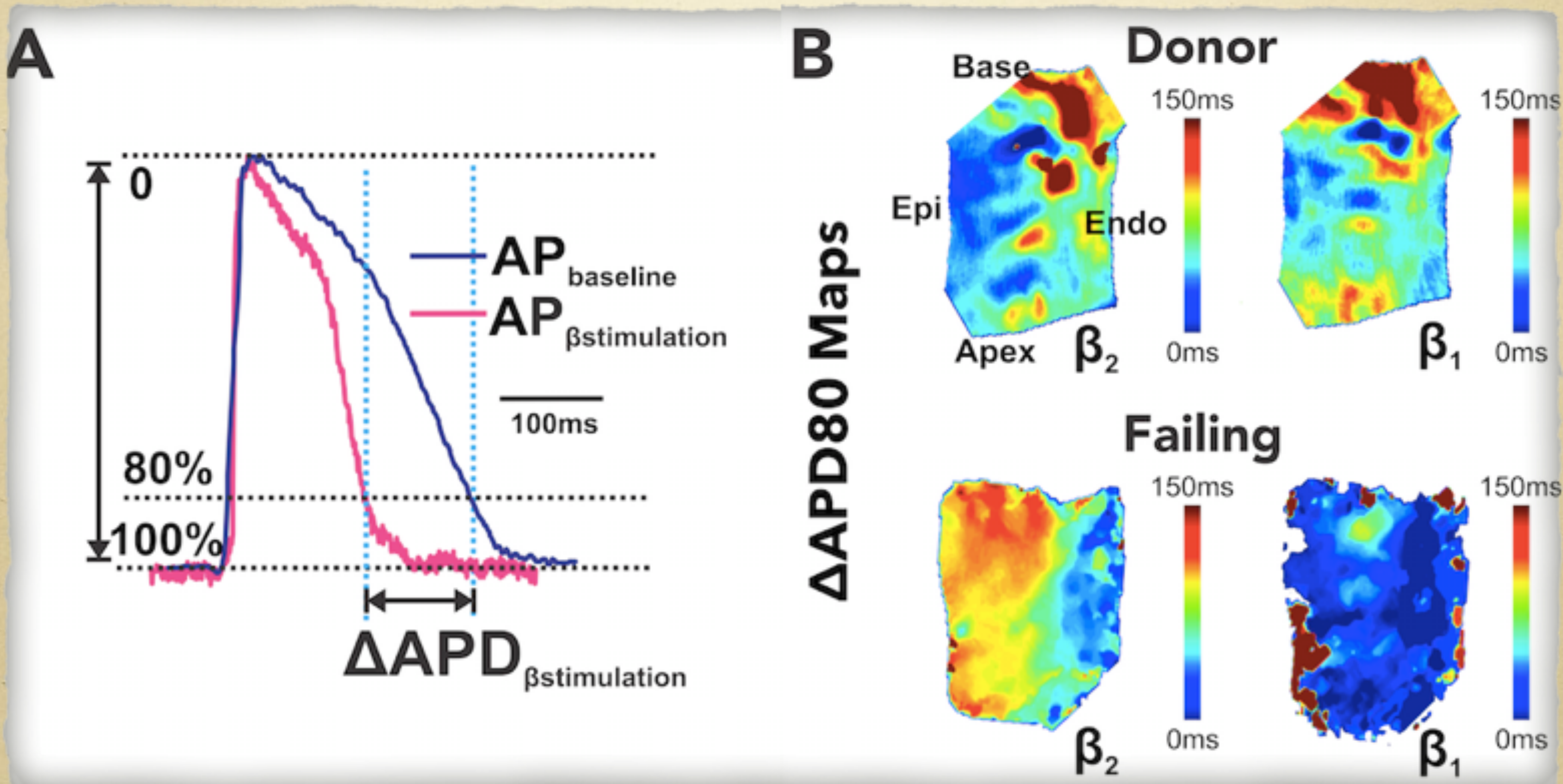


β_1 vs. β_2 adrenergic receptor remodeling in human failing heart



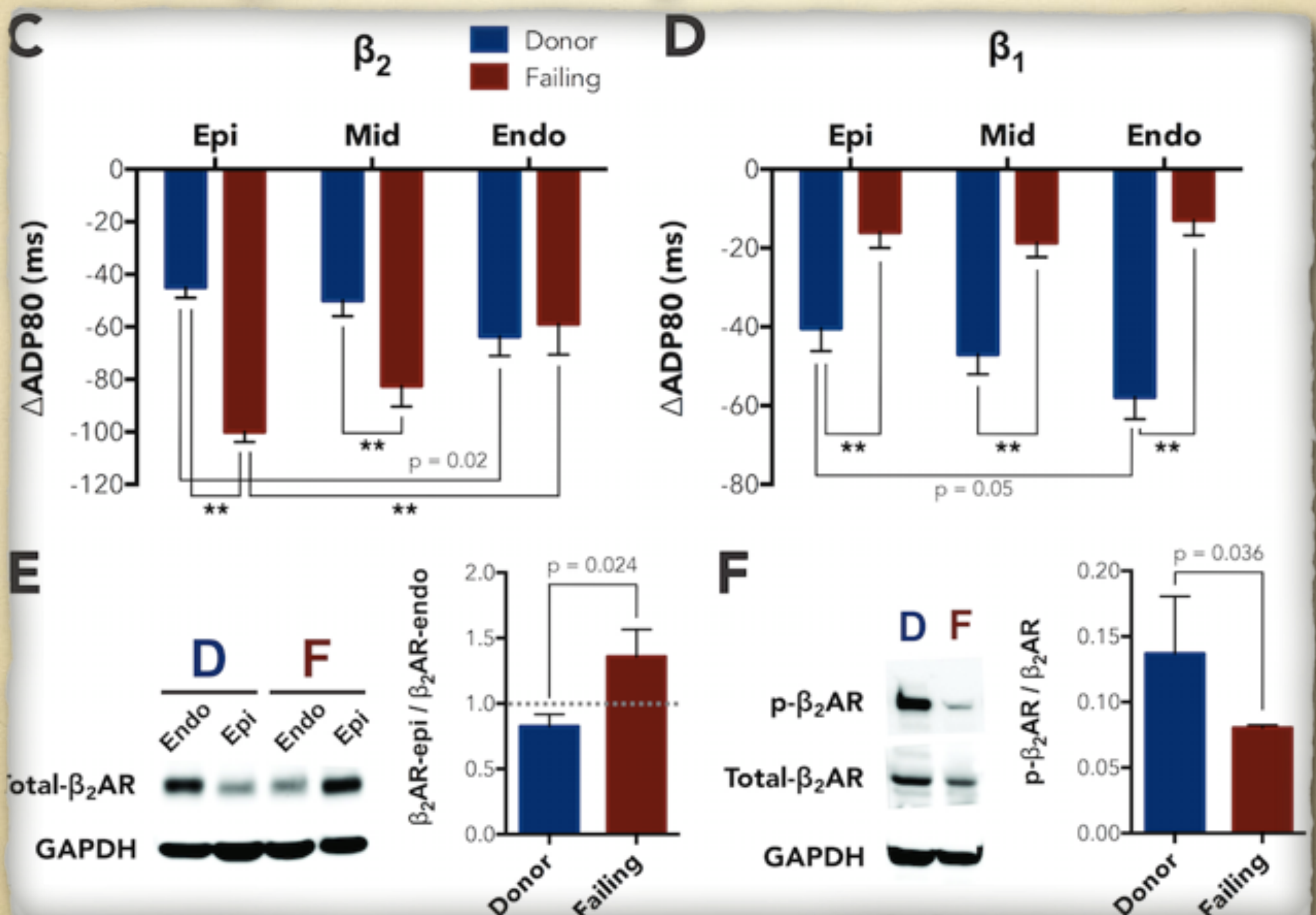
Lang, Circ: A&E, 2015

Action potential duration shortening due to β_1 vs. β_2 AR Stimulation



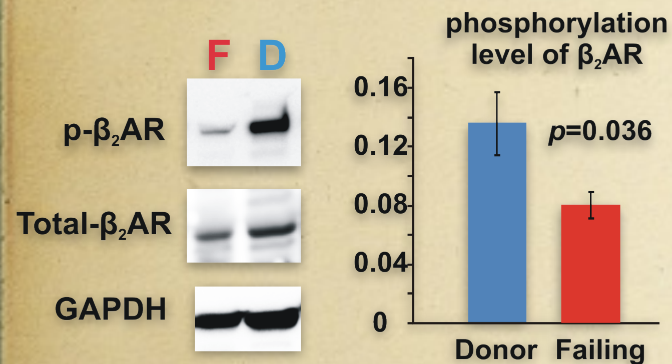
Lang, Circ: A&E, 2015

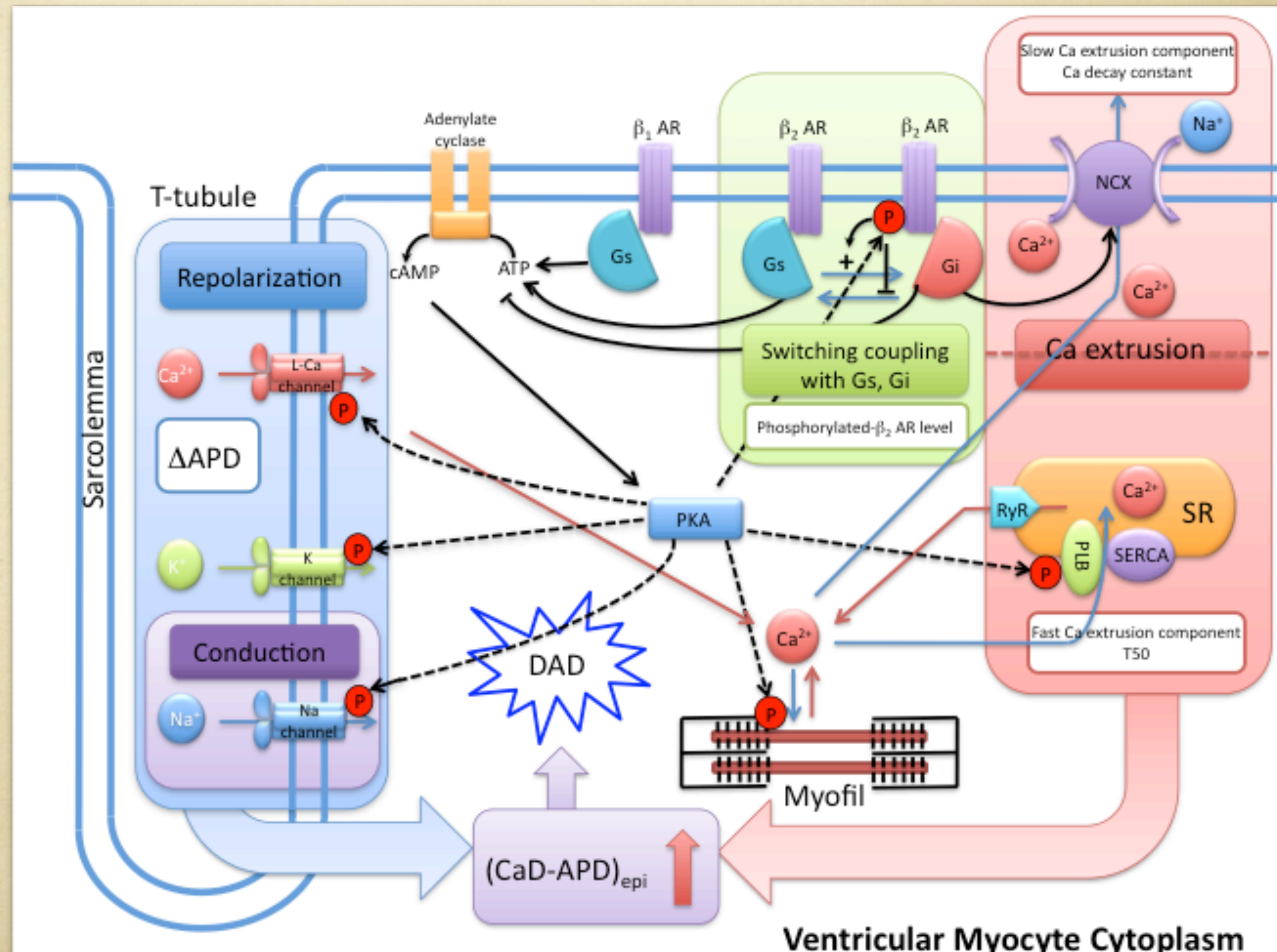
APD shortening due to β_1 vs. β_2 adrenergic receptor stimulation



Lang, Circ: A&E, 2015

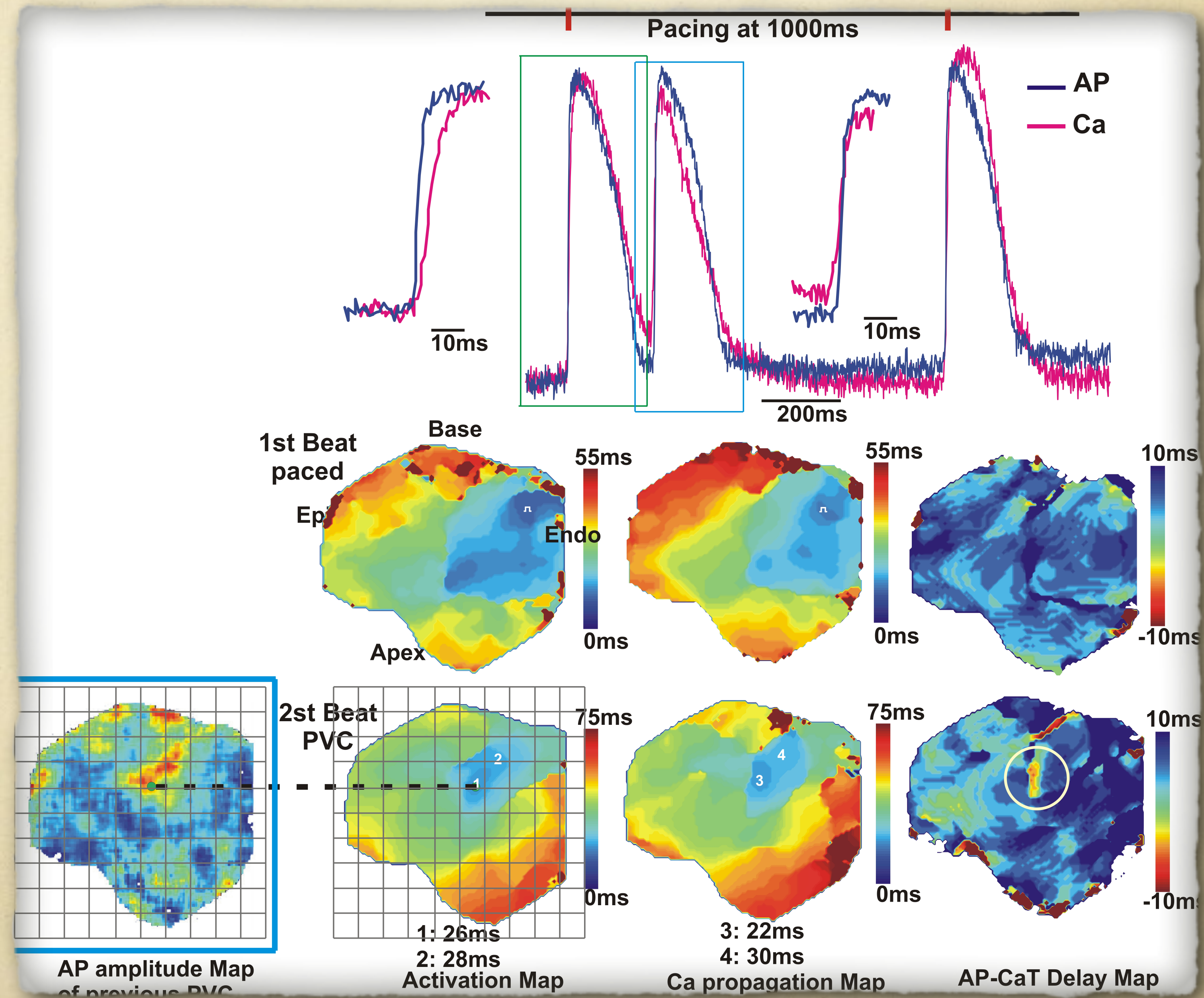
Switch of β2 AR from G_i to G_s in human heart failure





Lang, Circ: A&E, 2015

Ca-mediated arrhythmogenesis during β_2 stimulation in human heart failure



Lang, Circ: A&E, 2015

Challenges

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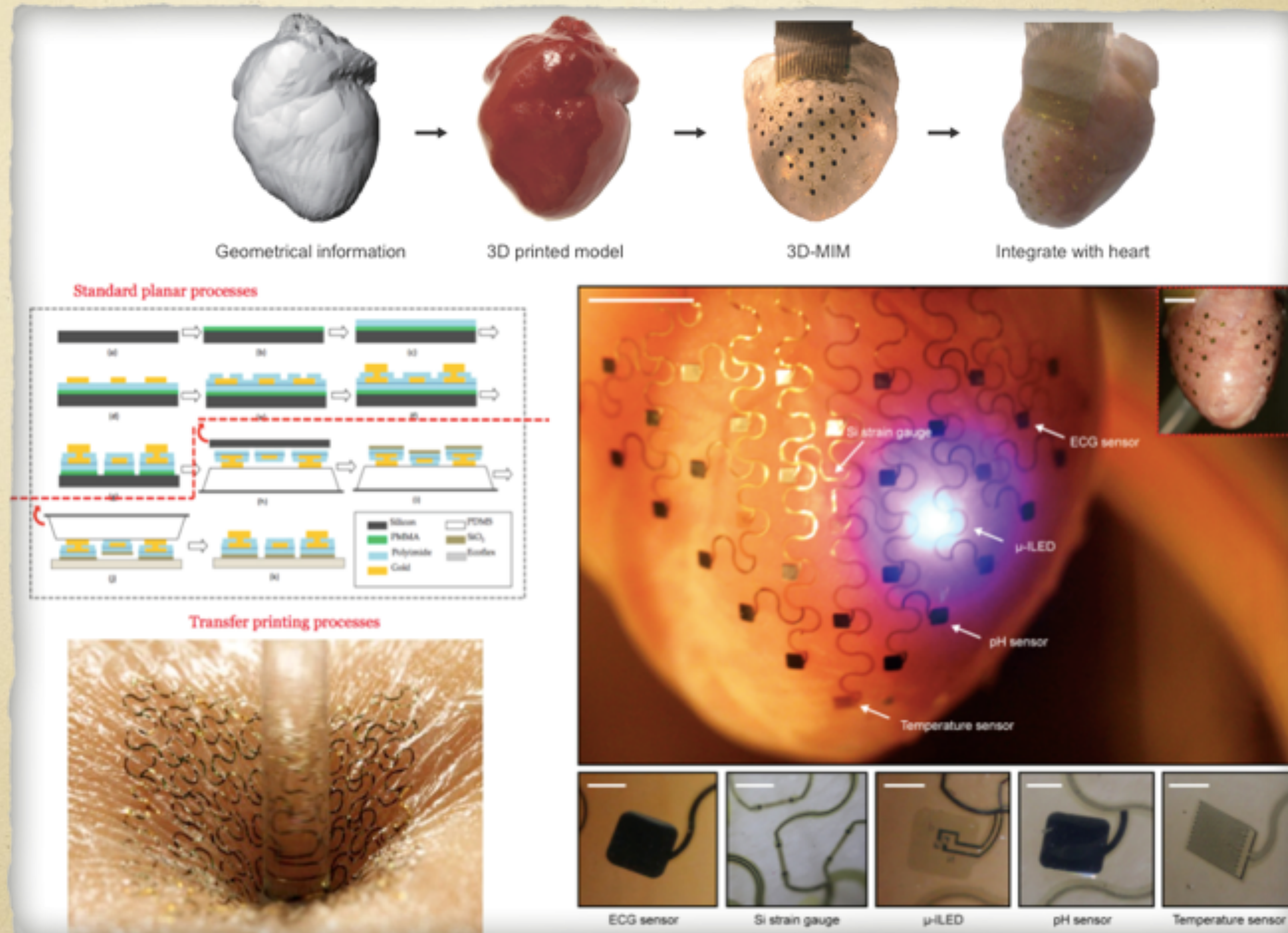
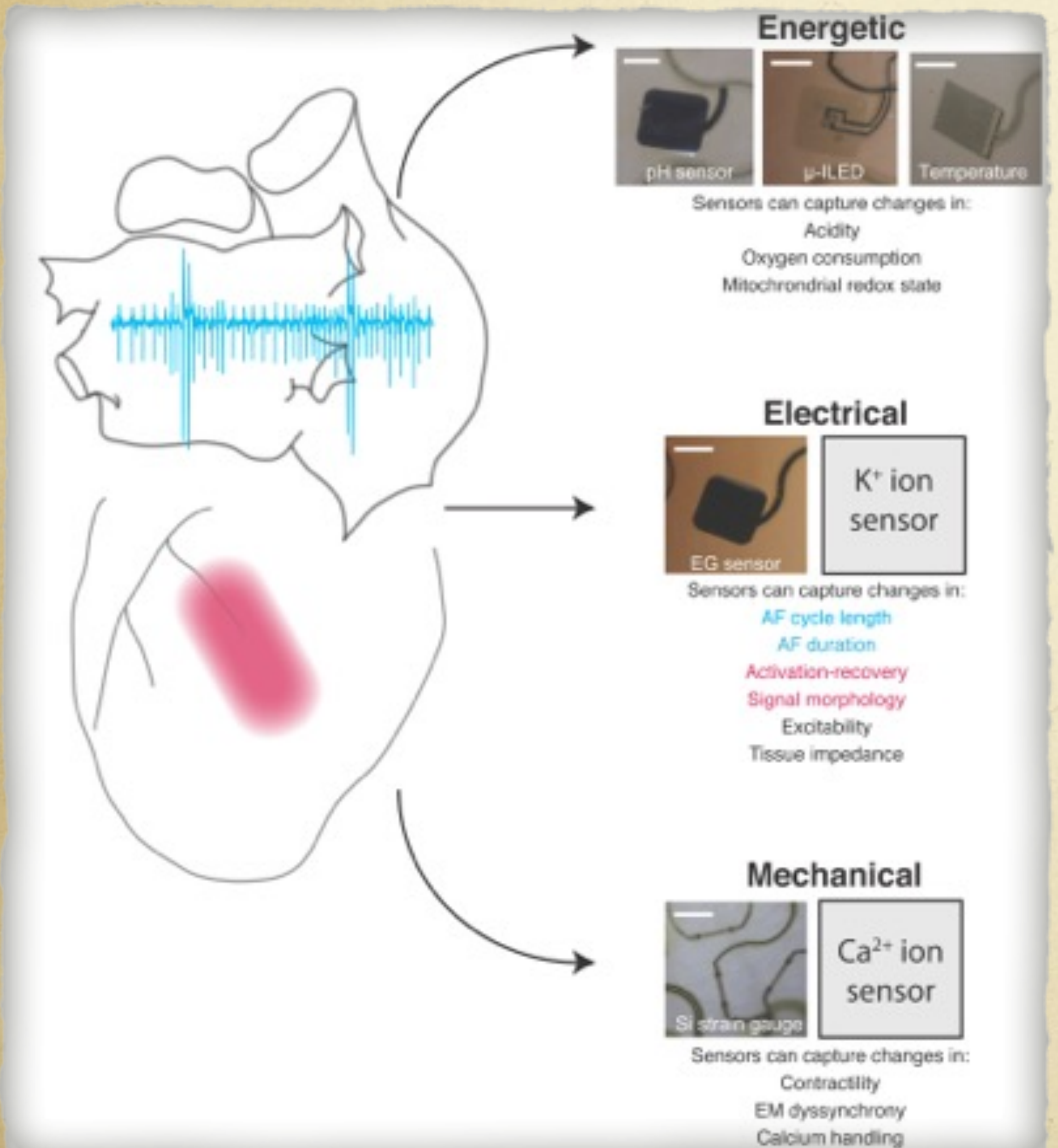
3D Multifunctional Integumentary Membranes (3D-MIMs) for spatiotemporal cardiac measurements and stimulation across the entire epicardium



Xu et al, Nature Comm. 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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- Mid-America Transplant Services, Saint Louis, MO