

# ICD Shocks-Related Heart Failure Worsening



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# Korean Heart Rhythm Society COI Disclosure

*Yukiomi Tsuji:*

The authors have no financial conflicts of interest  
to disclose concerning the presentation





## Clinical problem of ICD therapy in heart failure patients

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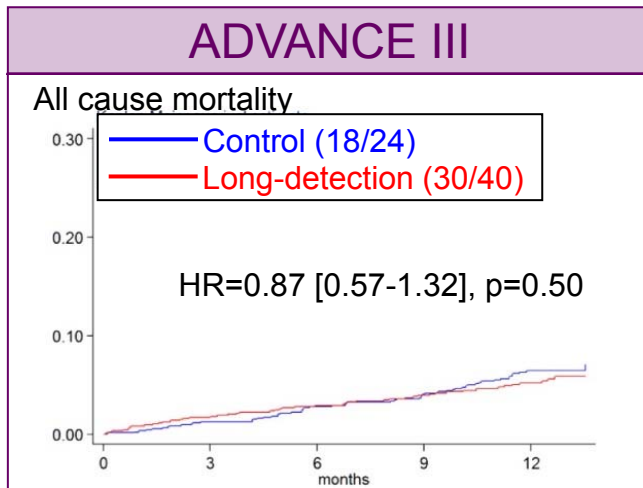
1. While implantable defibrillators (ICDs) can be life-saving, ICD shocks are associated with an increase in mortality and with worsening heart failure (HF).
2. Electrical storm patients receiving multiple shocks for repeated VT/VF have more serious consequences than those with isolated VT/VF unrelated to electrical storm .
3. It remains unclear, however, whether shocks play a causal role or whether this correlation is due solely to the underlying disease.





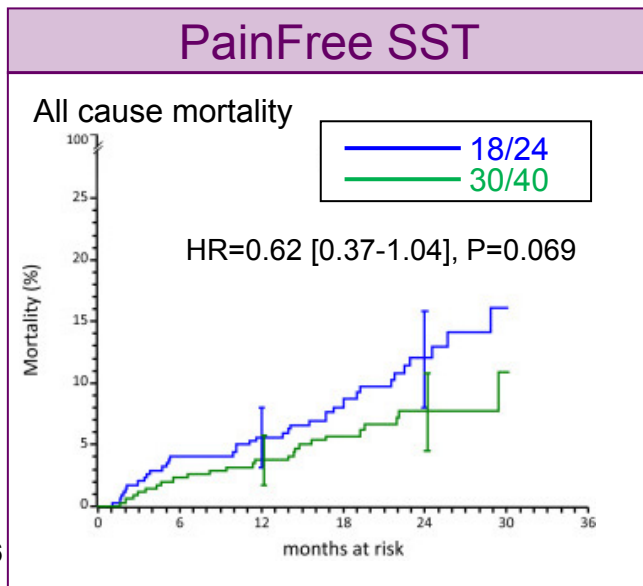
# A mortality benefit is NOT provided by currently used therapies

## ICD programming



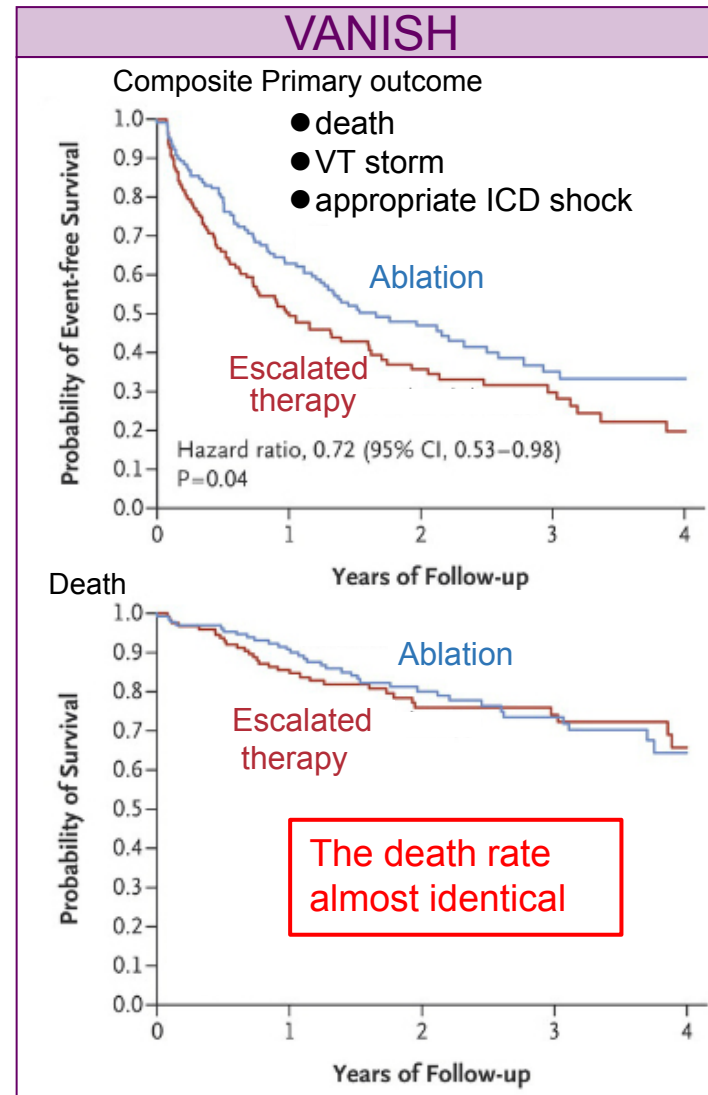
Gasparini M *et al.*  
JAMA 2013

## PainFree SST



Stems LD *et al.*  
Heart Rhythm 2016

## Catheter ablation



Sapp JL *et al.*  
N Engl J Med 2016



## Background and Aims

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1. Development of novel therapeutic approaches is required and desirable to reduce the risk of death associated with shocked VT/VF.
2. Lack of understanding of the underlying mechanisms strongly limits the success of ICD patient management.

Here we discuss mechanism-based therapeutic approach for shock related HF worsening.





## Harmful effects of electrical shocks

- Transient impairment of cardiac function
- Mild elevation of cardiac troponin-I levels
- Functional changes in mitochondria  
Serum lactate increases in coronary sinus.
- Pathological changes:  
Inflammation, fibrosis, calcification, macrophage infiltration, myocyte necrosis, and interstitial edema
- Ultrastructural alterations:  
Mitochondrial swelling, loss of membrane integrity, and mitochondrial crest disruption



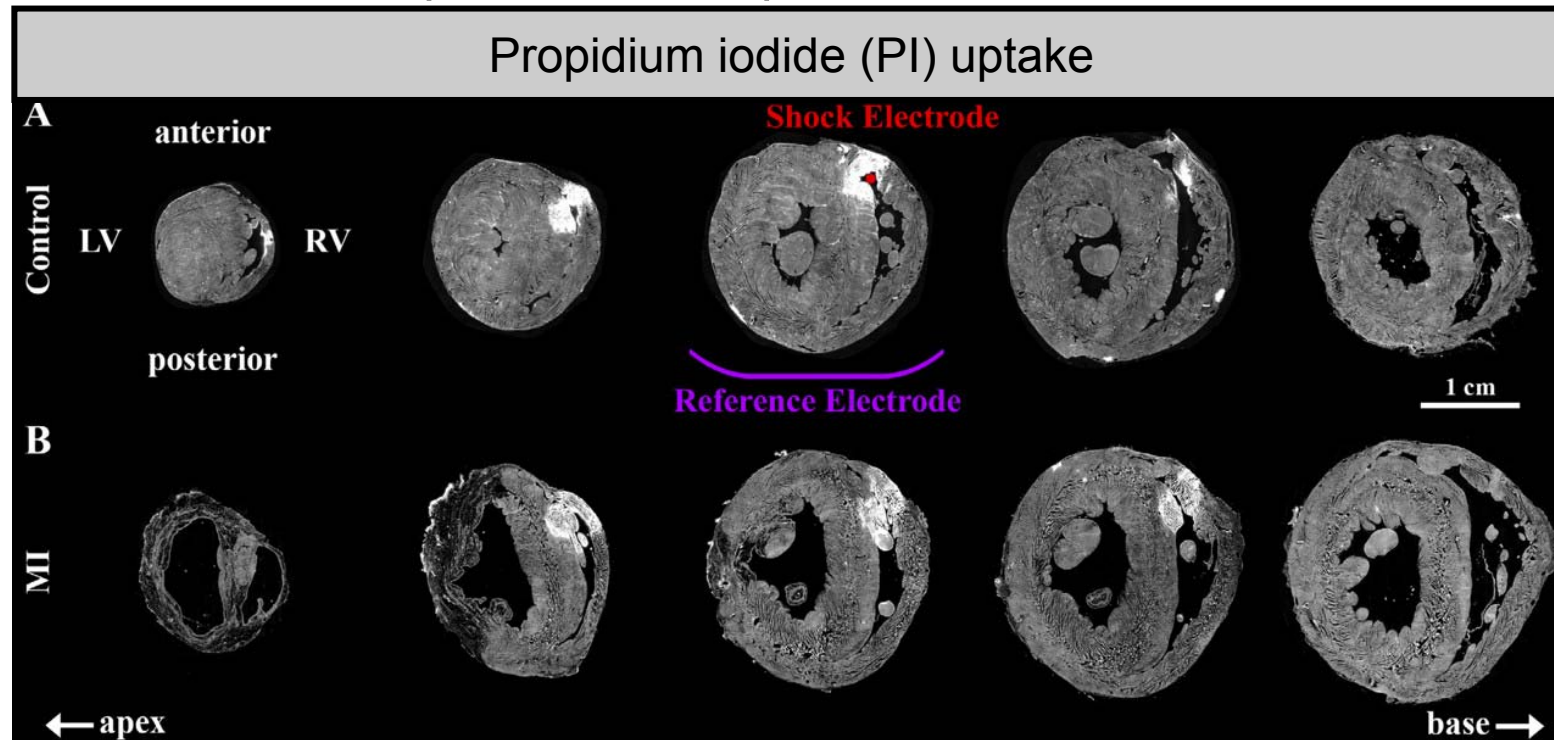
Electroporation due to electrical shocks





# Shock-induced electroporation occurs at limited regions

Electroporation: disruption of cell membranes



- The PI staining limited around a RV shock-electrode; the area **only ~4%** of the whole ventricles
- It was comparable between normal and infarct hearts.





# Pathophysiology of HF

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## Metabolic remodeling Mitochondria dysfunction

- Impaired cardiac energetics
- Oxidative stress and structural remodeling
- Mitochondrial reactive oxygen species (ROS)

## Sarcoplasmic reticulum (SR) dysfunction

- RyR2 dysregulation
- Ca<sup>2+</sup>-pump depression

## Cytosolic Ca<sup>2+</sup>-overload

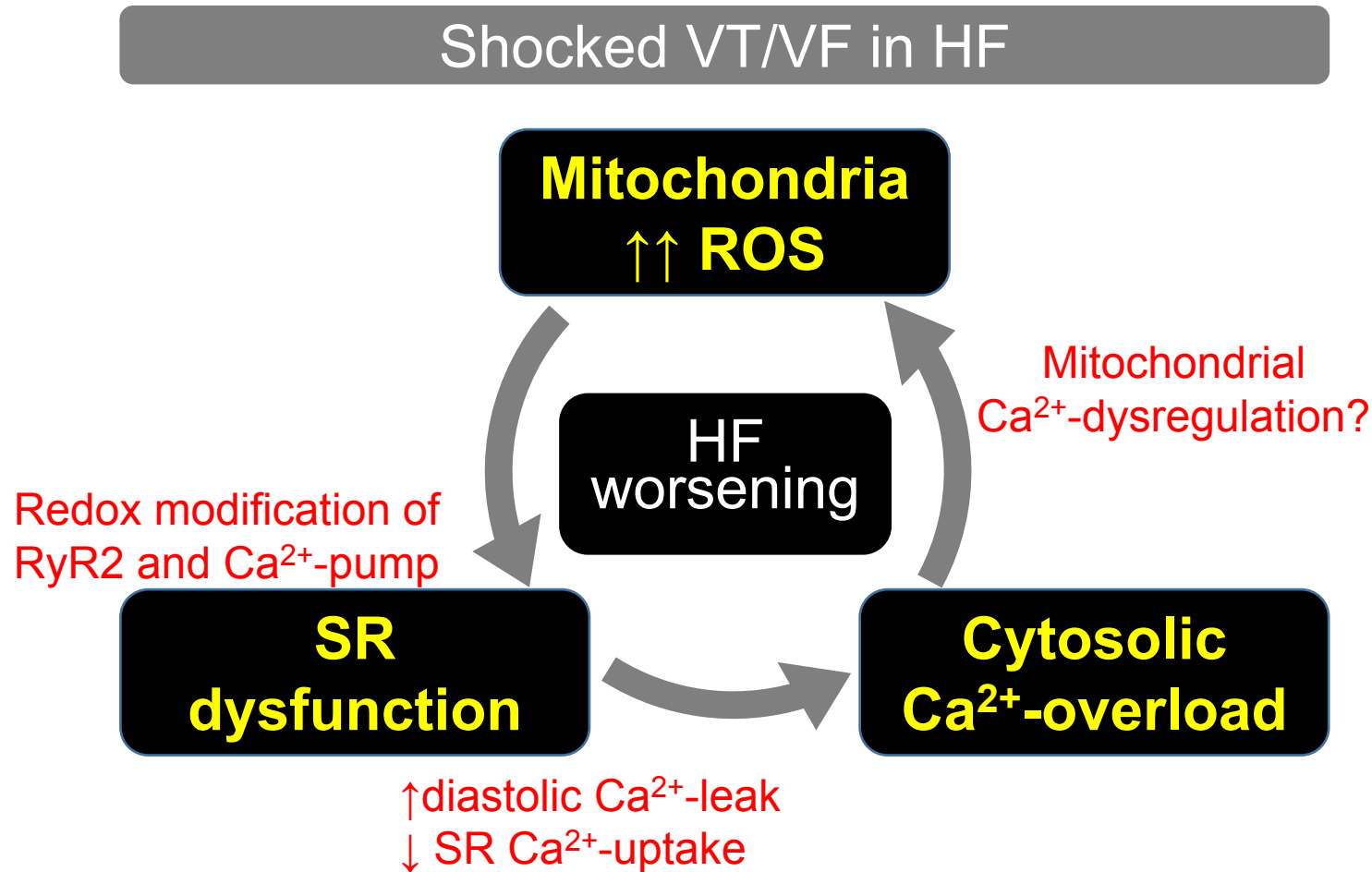
- DAD-triggering arrhythmias
- Ca<sup>2+</sup>-related signal pathways







# Hypothesis "mitochondria-SR-Ca<sup>2+</sup> positive feedback loop"



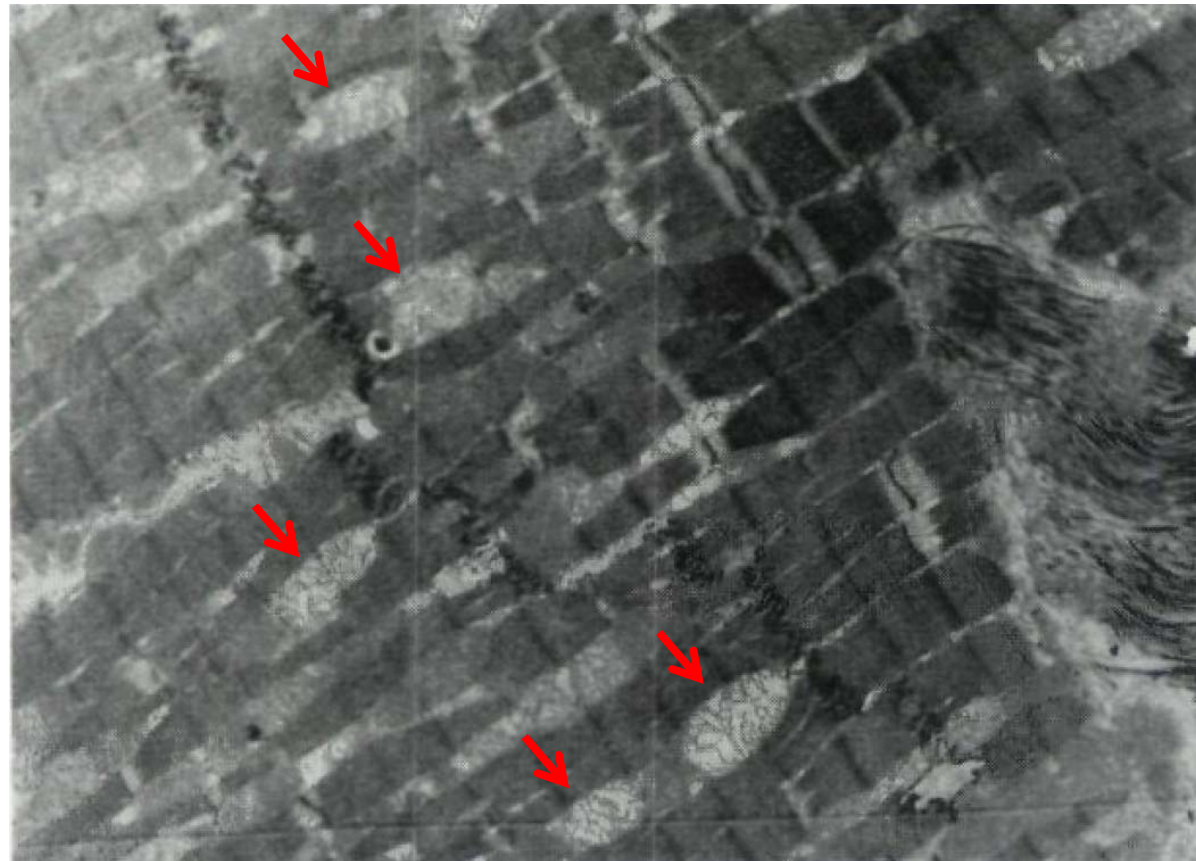


# Mitochondria are the main source of ROS

## Ultrastructural changes by multiple low energy endocardial countershocks

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Swollen mitochondria and disruption of mitochondria crests  
in the canine LV sample



Schirmer U *et al.* Pacing Clin Electrophysiol 1997

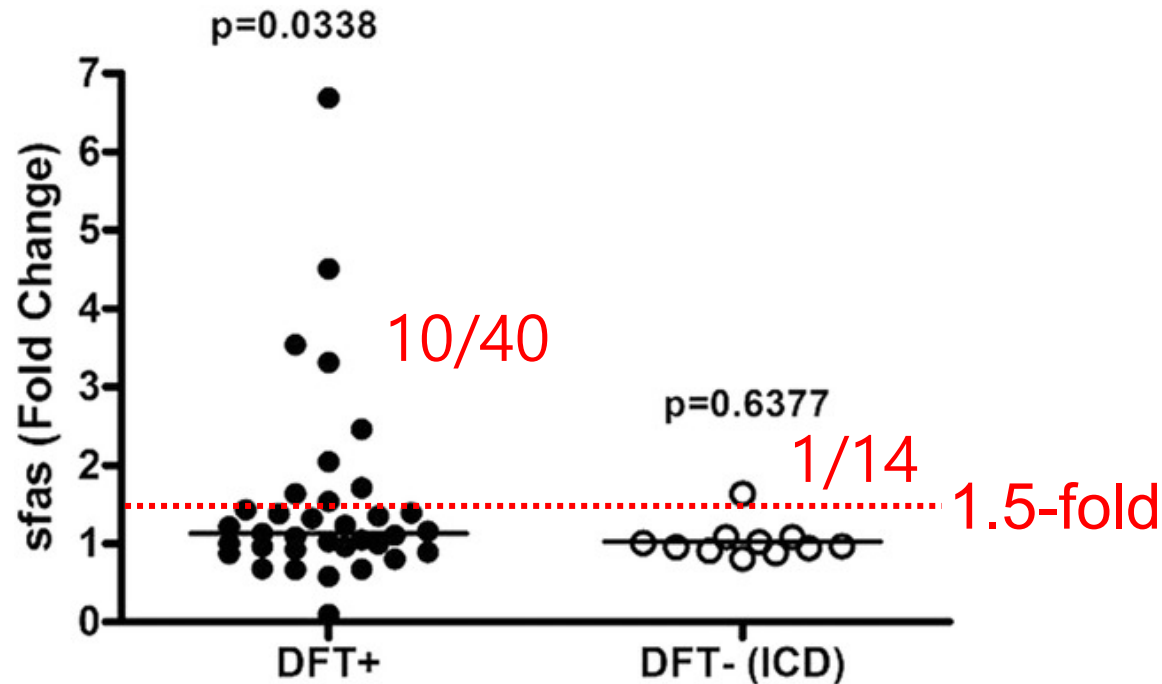




# Mitochondria are the main source of ROS

## Apoptotic signaling is activated by ICD-shocks in HF patients

Serum levels of *sFas*, a biomarker of apoptosis  
24 h after defibrillation test

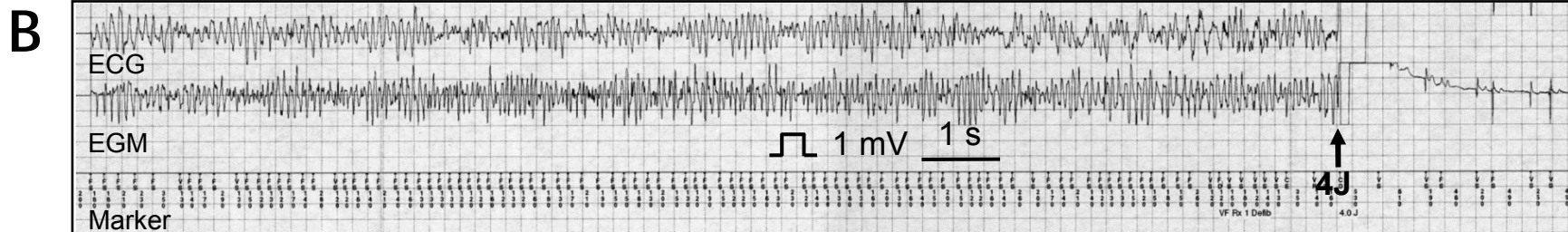
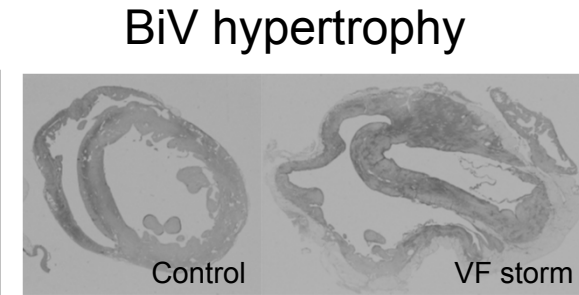
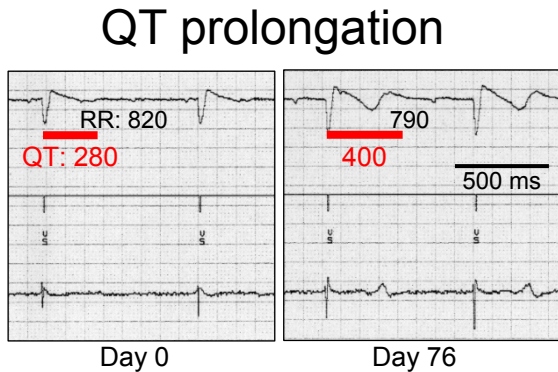
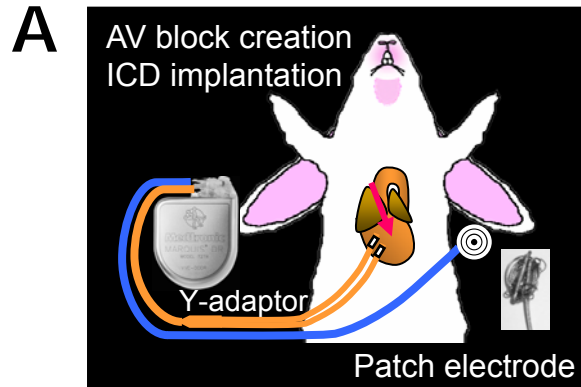


Brewster J *et al.* Pacing Clin Electrophysiol 2017





# Rabbit model of VF storm



Type	ATP Seq	Shocks	Success	ID#	Date	Time hh:mm	Duration hh:mm:ss	Avg bpm A/V
VF	0	4J	Yes	25555	16-Sep-2016	06:47	:01:41	—/333
VF	0	4J	Yes	25405	16-Sep-2016	04:39	:11:22	—/286
VF	0	4J	Yes	25174	16-Sep-2016	01:57	:02:22	—/375
VF	0	4J	Yes	24781	15-Sep-2016	22:03	:08	—/333
VF	0	4J	Yes	24696	15-Sep-2016	15:29	:01:04	—/333
VF	0	4J	Yes	24237	14-Sep-2016	15:48	:12:30	—/375
VF	0	4J	Yes	24110	14-Sep-2016	11:36	:04:47	—/188
VF	0	4J,7J	Yes	23861	14-Sep-2016	06:20	:03:50	—/429



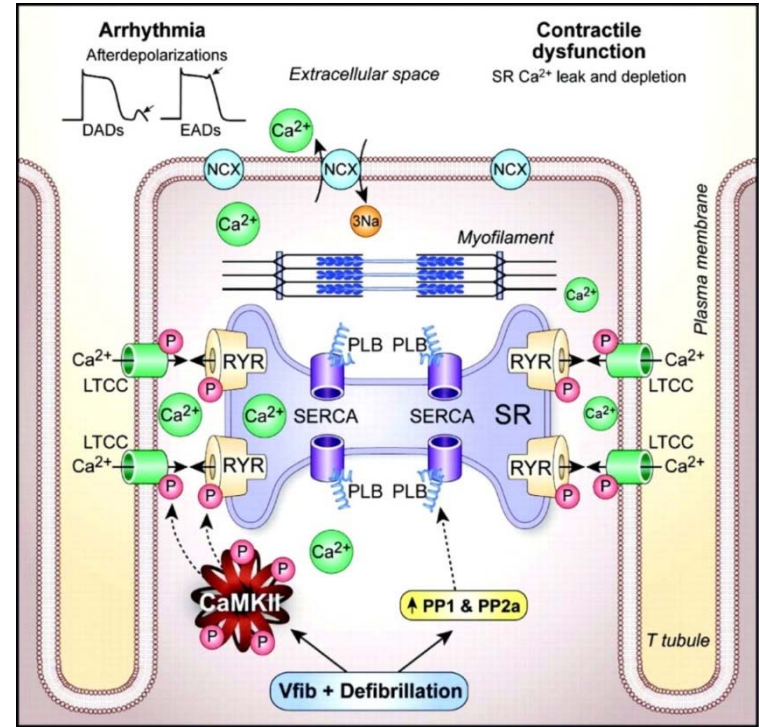
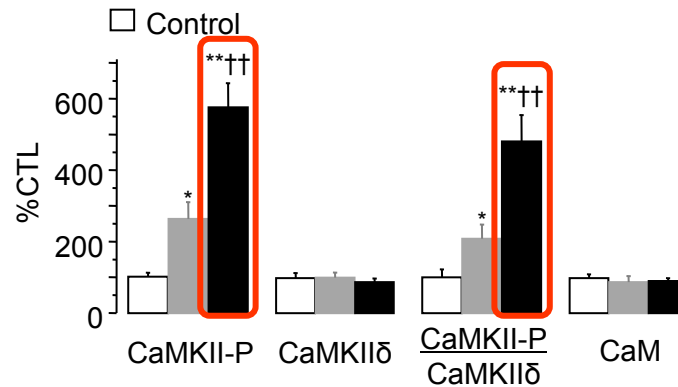
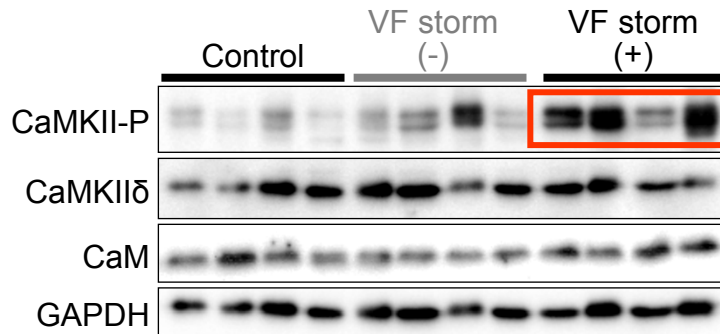
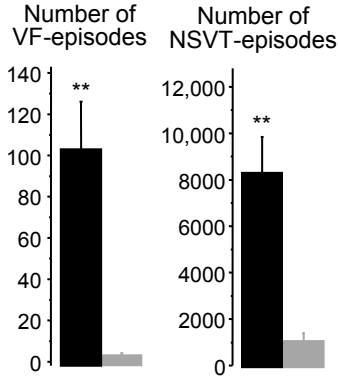
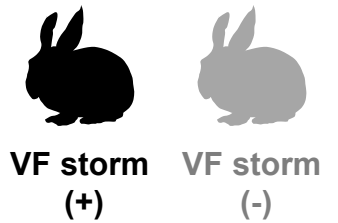


# Connection between VF storm and CaMKII

VF storm developed in 50%

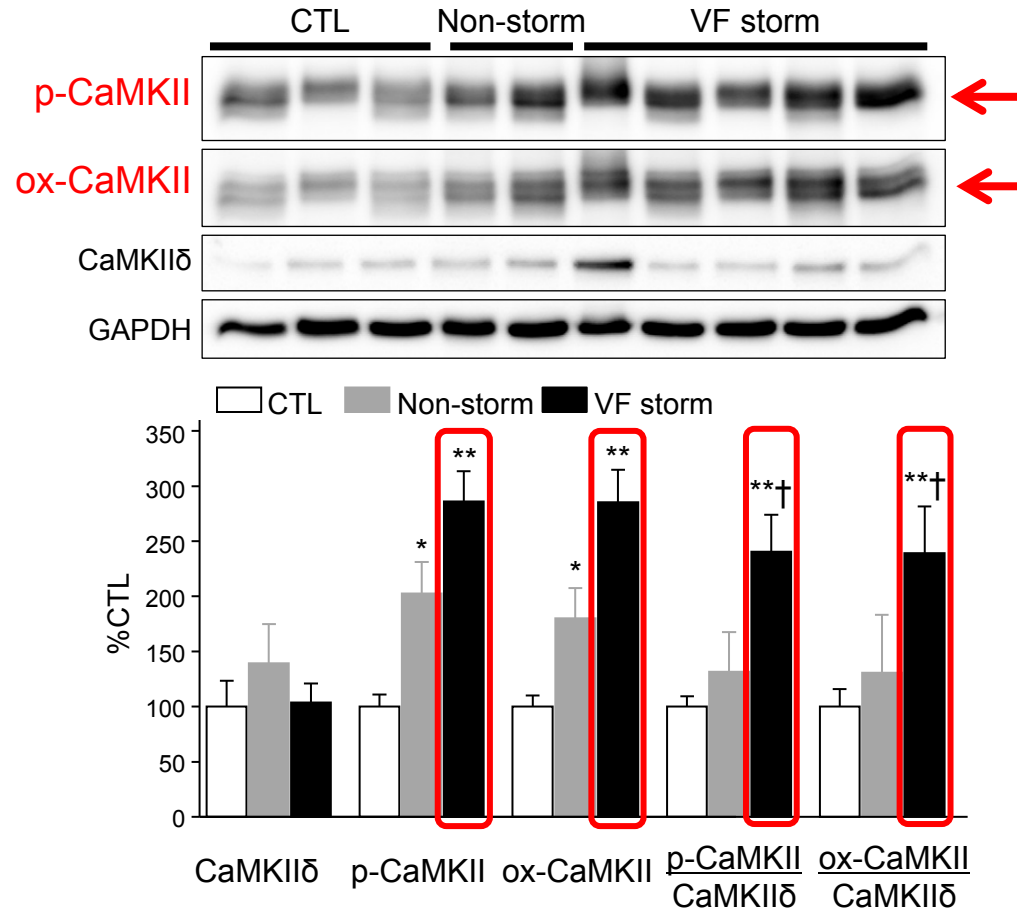
Striking upregulation of phosphorylated form of CaMKII

Phosphorylation abnormalities of Ca<sup>2+</sup>-handling proteins





# Oxidized CaMKII is also upregulated in VF storm rabbits



\*p<0.05, \*\*p<0.01 vs. CTL; †p<0.05 vs. non-storm

Tsuji Y *et al.* HRS2018; AHA2018

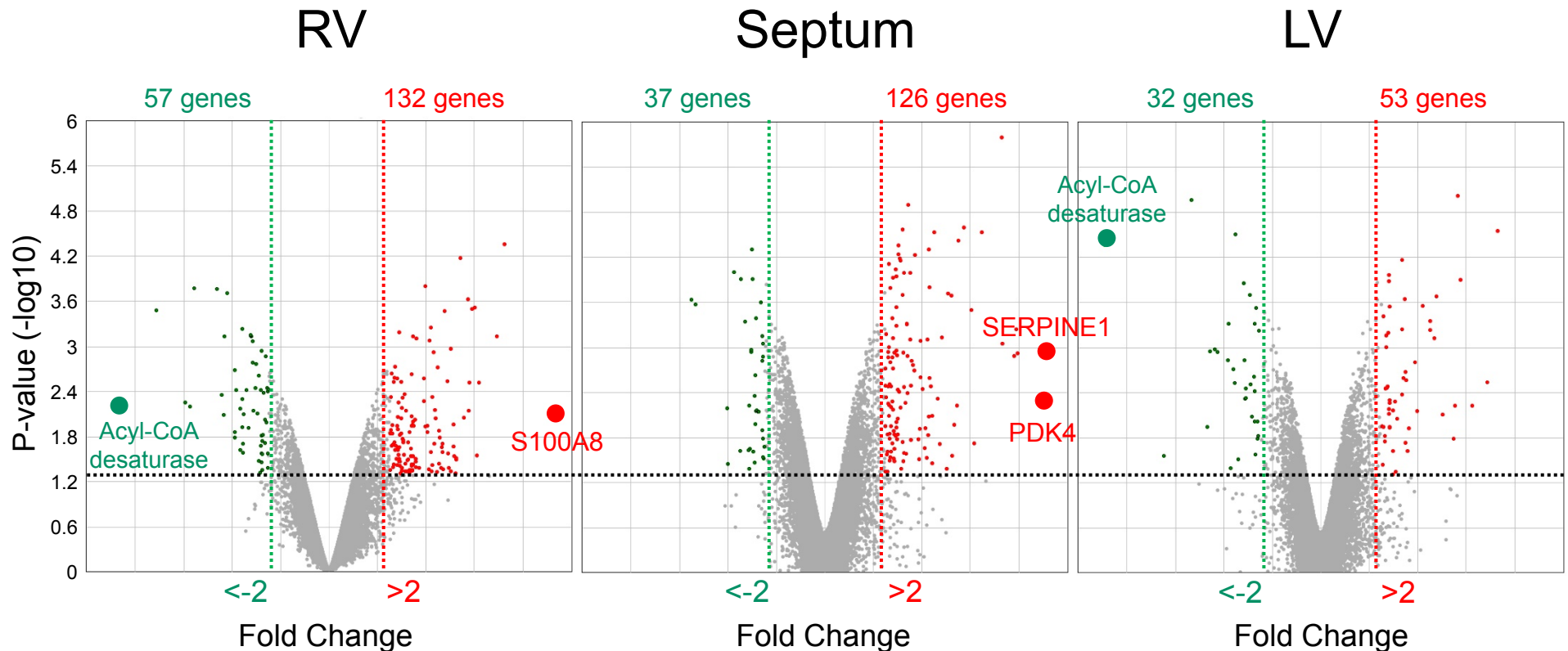
**ROS production is enhanced and Ca<sup>2+</sup>-levels are elevated in association with VF storm.**





# Regional gene expression changes

**Preliminary data in 3 VF storm vs. 2 control hearts**  
(GeneChip™ Rabbit Gene 1.0 ST Array)

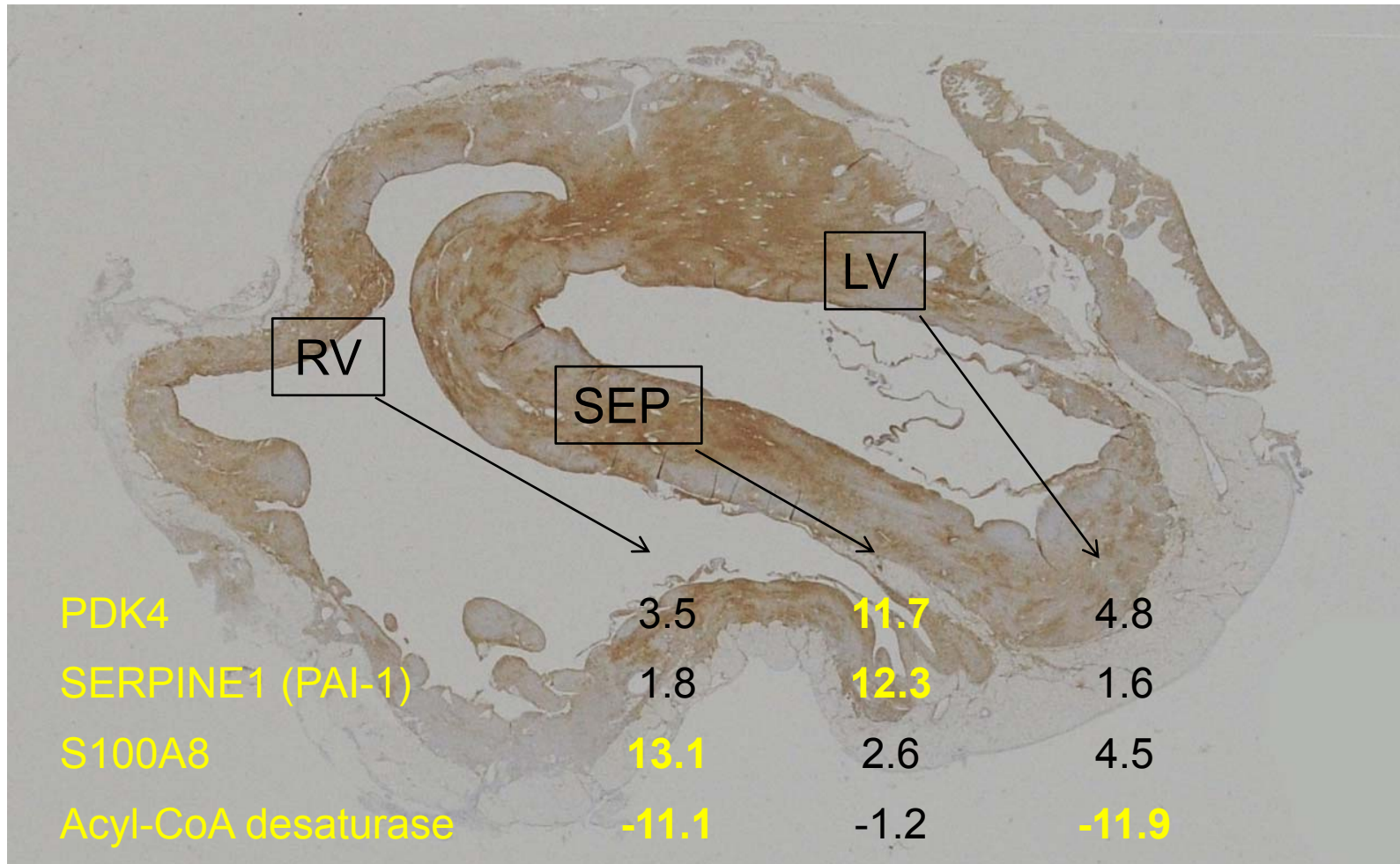


SERPINE1 = plasminogen activator inhibitor 1 (PAI1)  
PDK4 = pyruvate dehydrogenase kinase 4  
S100A8 = S100 calcium binding protein





## 4 gene transcripts with >10- or <-10-fold changes



Fold changes for VF storm vs. control rabbits



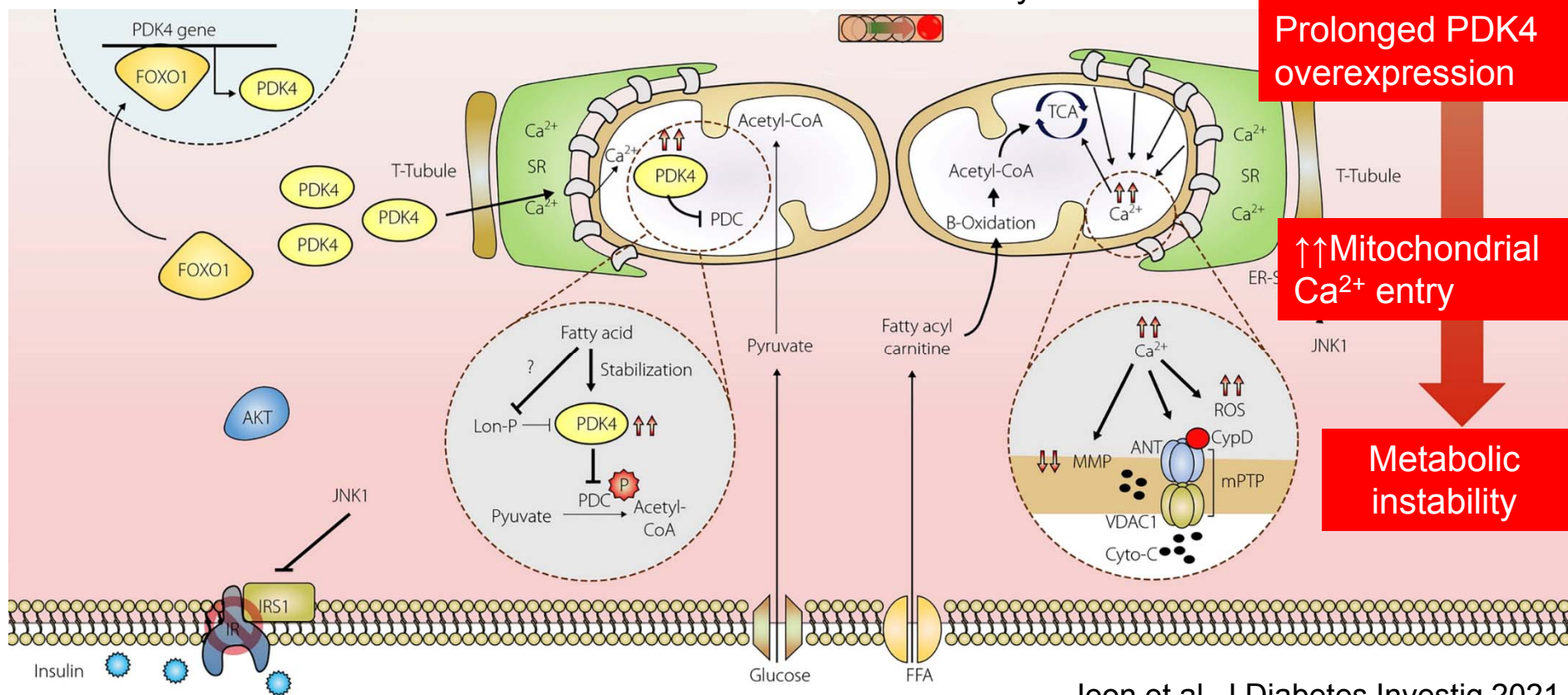




# Loss of metabolic flexibility as a result of PDK4 upregulation

PDK4 regulates the metabolic switch in skeletal muscle.

Glucose oxidation  $\longrightarrow$  Fatty acid oxidation



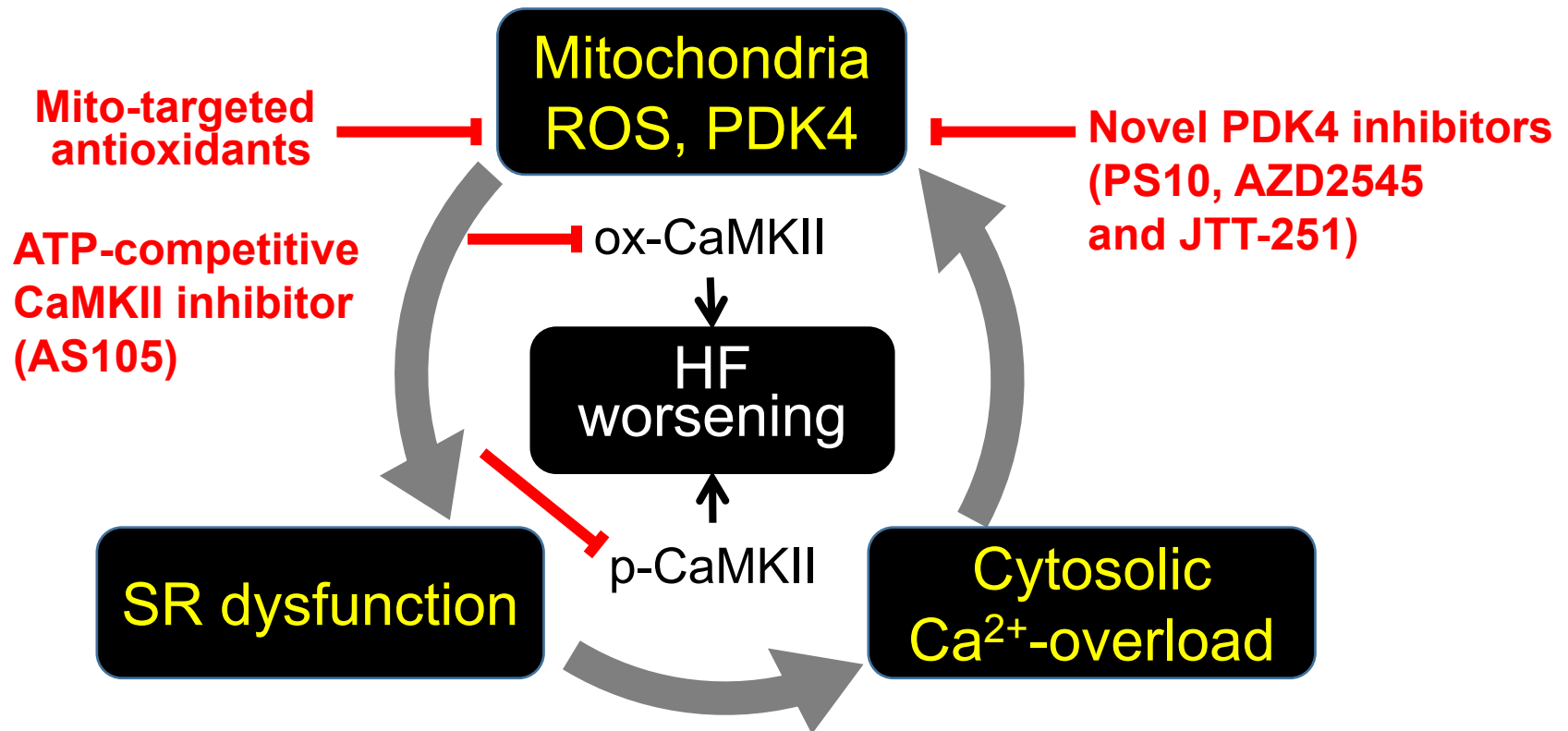
Diabetes, cancer, non-alcoholic fatty liver disease, cancer-induced cachexia, sepsis, and amyloid lateral sclerosis





# Therapeutic targets against HF worsening by ICD shocks

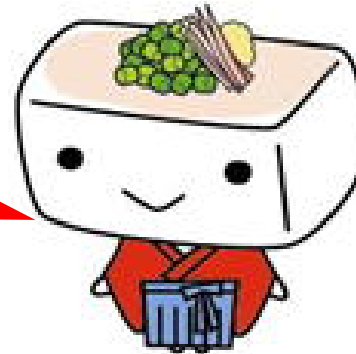
Shocked VT/VF in HF  
adrenergic surge / electroporation / arrhythmic burden





# Thank you!

감사드립니다



Official Mascot  
Nagasaki University

