Arrhythmogenesis and Antiarrhythmic Drug Therapy in Congestive Heart Failure

Prevalence and prognosis

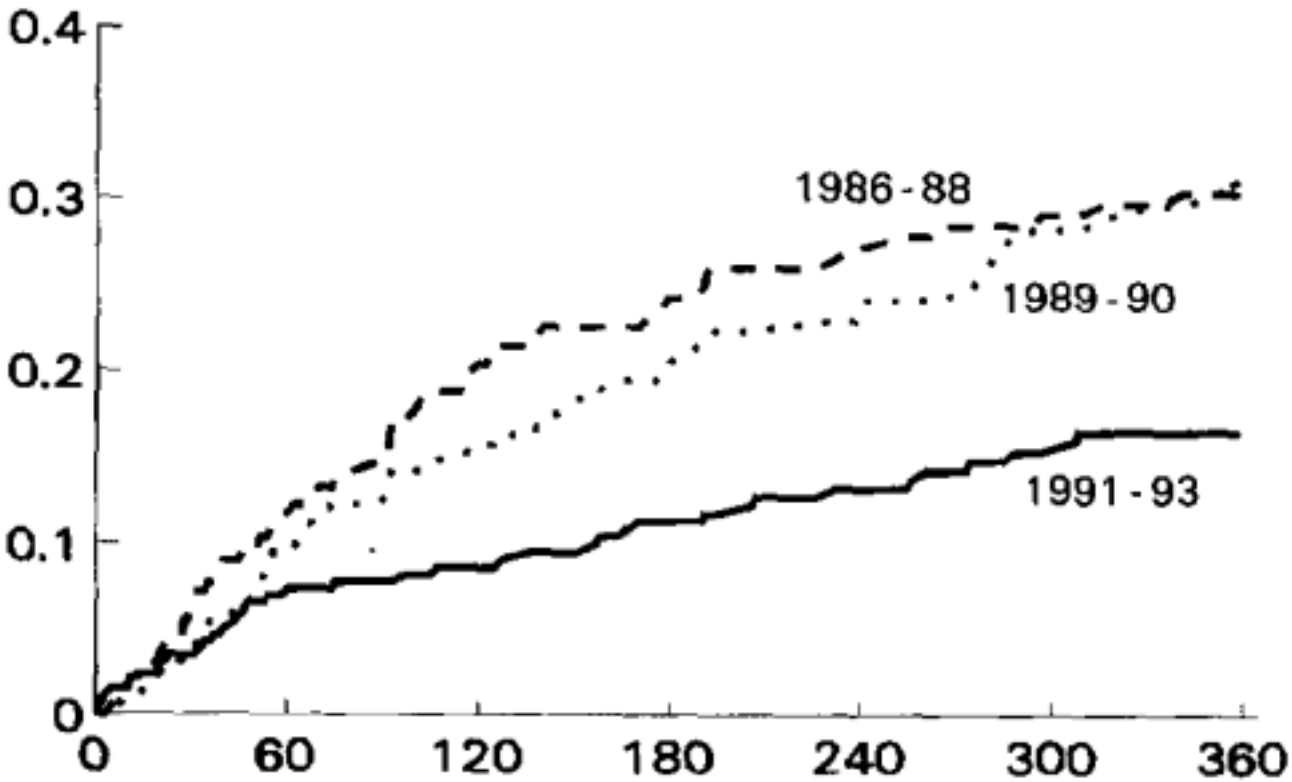
Approximately 1 - 2% of the US population,

:approximately 2 to 3 million people suffer from CHF

Approximately 250,000 to 400,000 new cases, reported annually

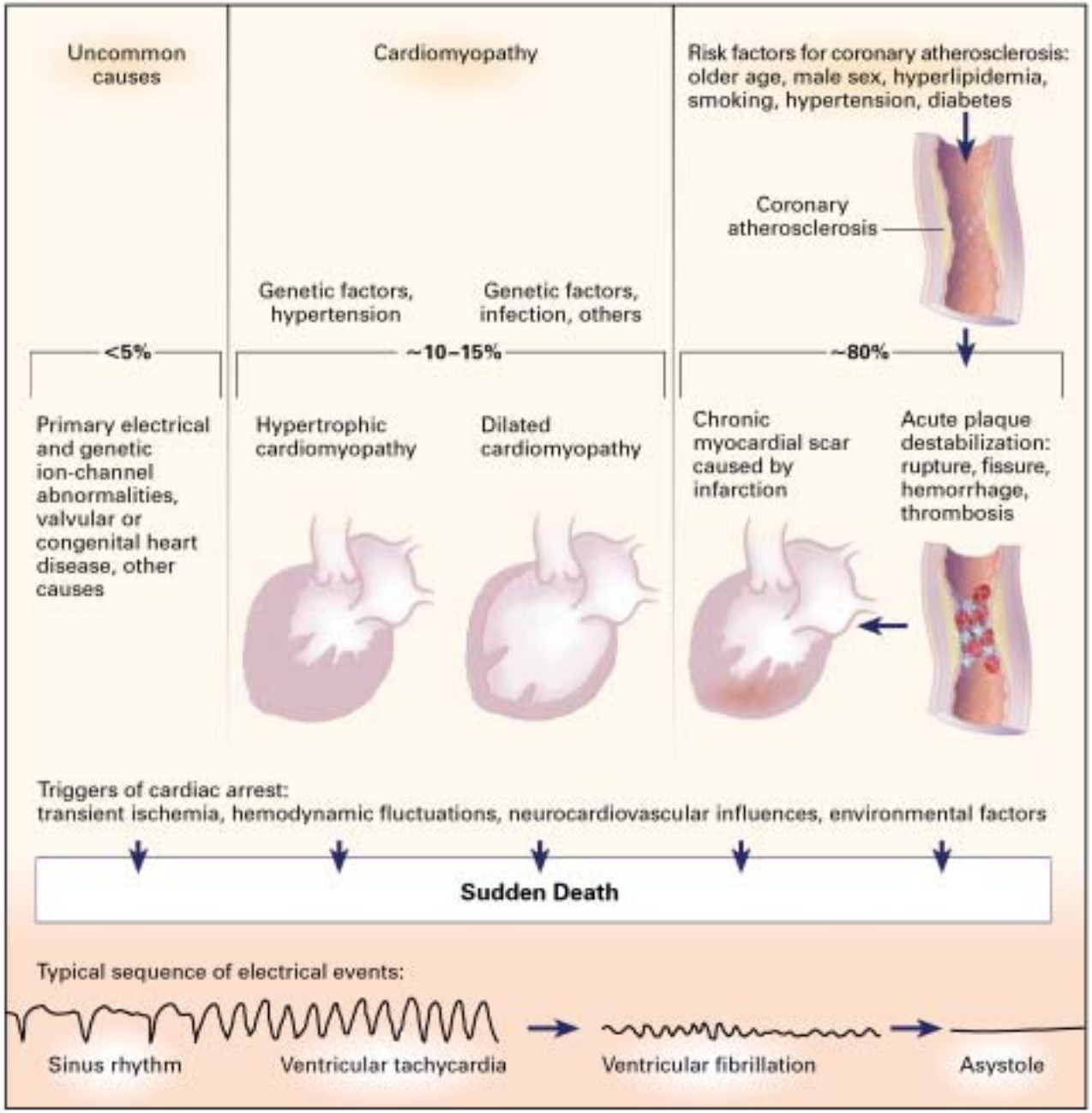
50% to 60% of deaths in patients with CHF are sudden and are attributed to an arrhythmic cause, most often to ventricular tachyarrhythmia.

Cumulative deaths from all causes



1986-88	168	133	115	107
1989-90	179	141	114	91
1991-93	222	189	162	131

JACC 1995;26:1417



SUDDEN DEATH DUE TO CARDIAC A RRHYTHMIAS

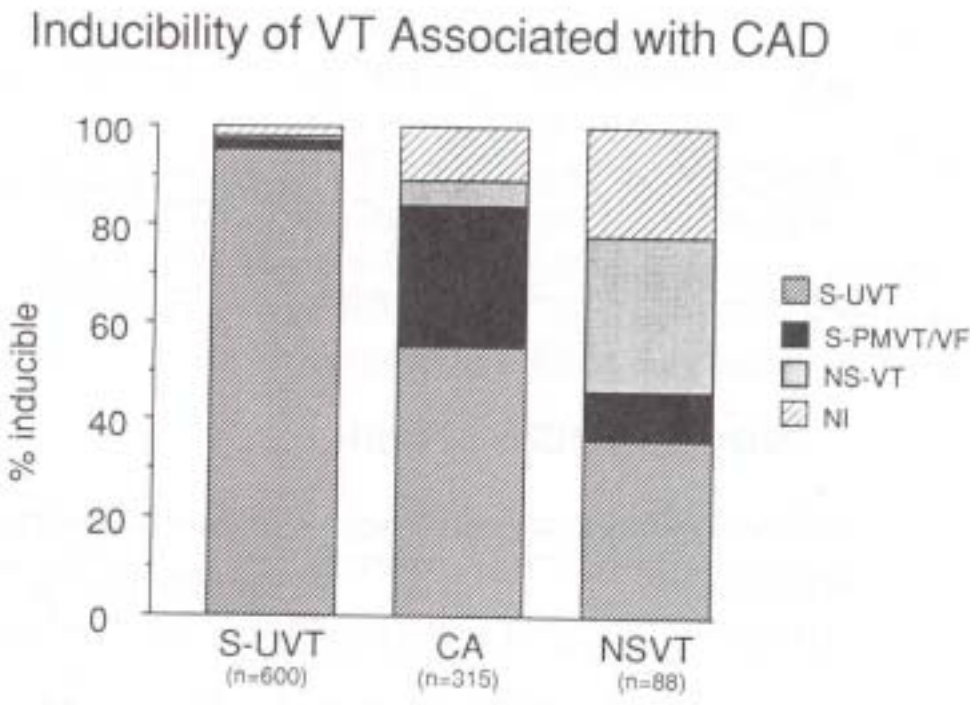
HEIKKI V. HUIKURI , M.D., NEJM 345:1473, 2001

Multiple mechanisms of sudden death in CHF

VT or VF
EMD
Bradyarrhythmias

Approx. ½ of all unexpected death in hospitalized CHF pt
: bradyarrhythmia or EMD

EMD : pulmonary emboli, AMI
Bradyarrhythmia : conduction system disease, AMI, hyperkalemia



Clinical Cardiac Electrophysiology, Josephson ME

Table 1. *Types of inducible arrhythmias in patients with dilated cardiomyopathy: Relationship to the spontaneous arrhythmia presentations*

	Induced arrhythmia		
Arrhythmia presentation	NSVT	PMVT/VF	SMVT
NSVT	~40–45%	~0–30%	~0–15%
Cardiac arrest	~20%	~30%	~10–15%
SMVT	–	–	~75–100%

NSVT: Nonsustained VT; PMVT/VF: Polymorphic VT or ventricular fibrillation; SMVT: Sustained monomorphic VT.

Electrophysiology Studies in Patients with DCM
CER 2002;6:472–481

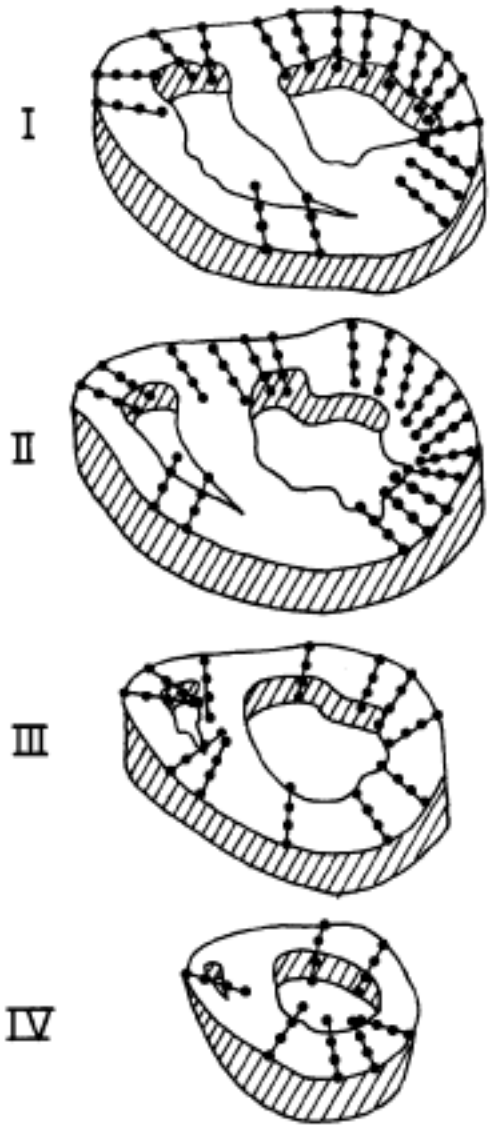
Reentry

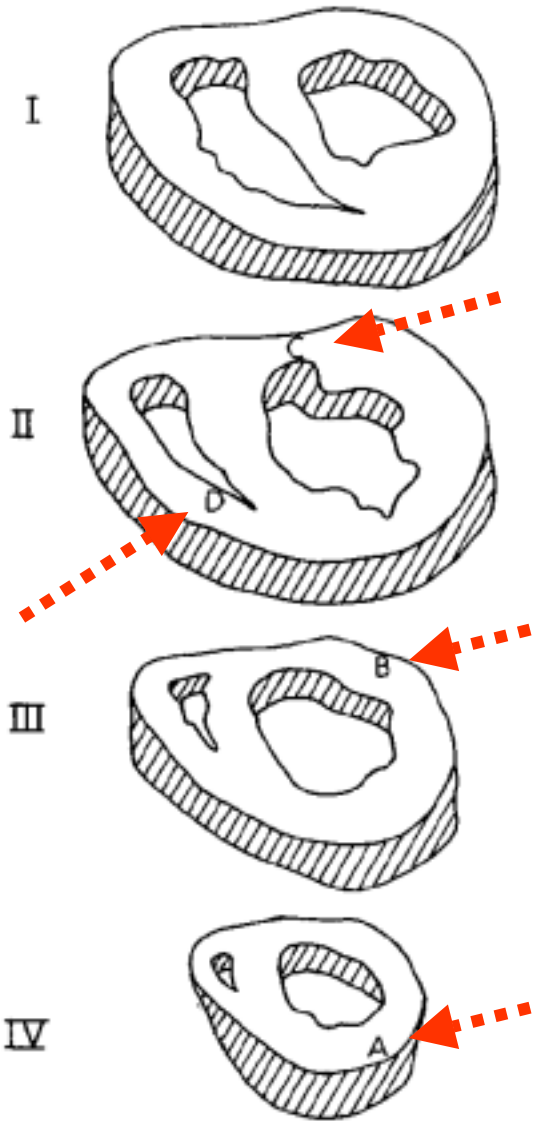
- **anatomic (scar-related, BBR)**
- **functional**

Focal

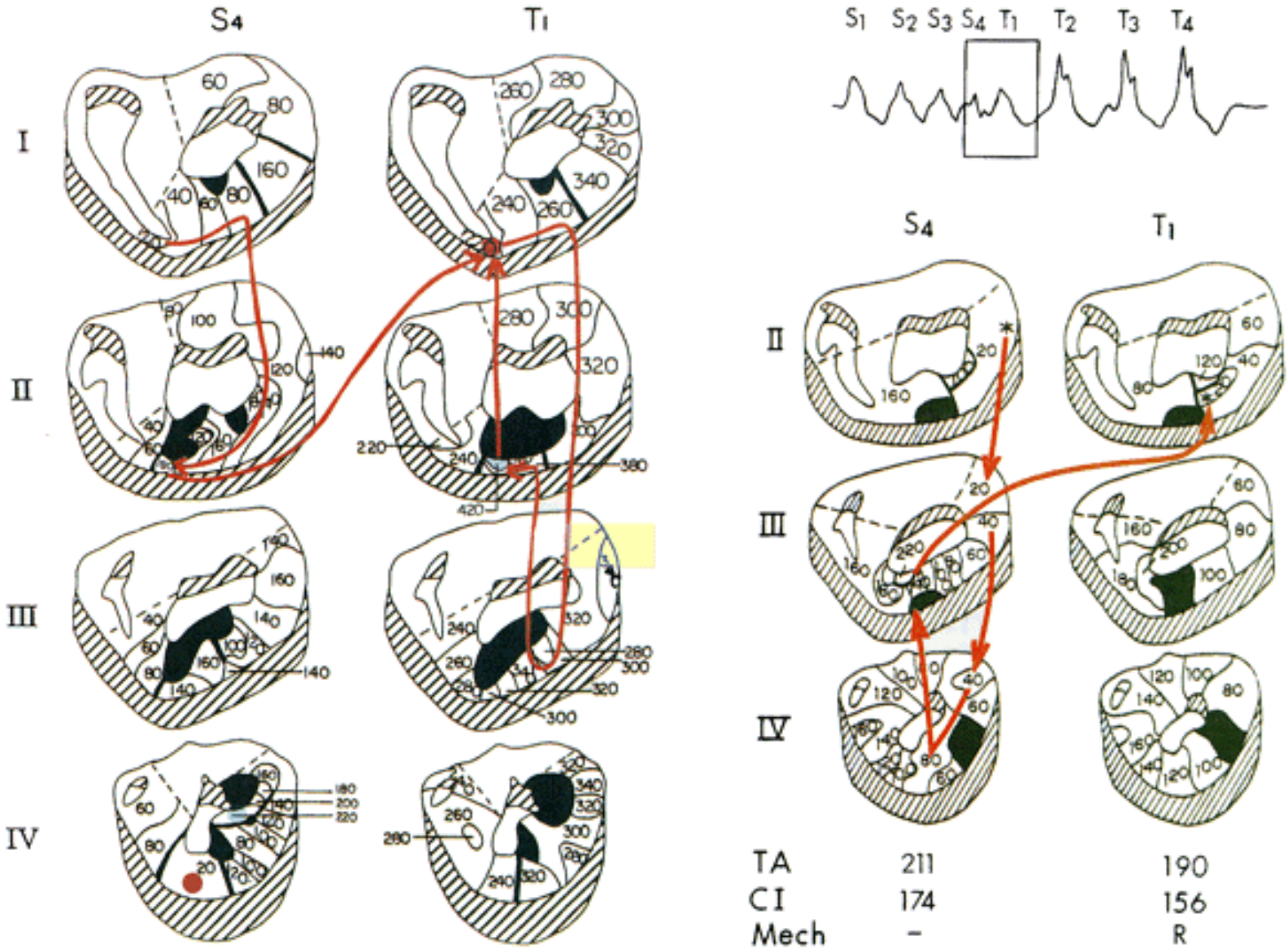
- **triggered activity**
- **automatic**

Circulation. 1998 Dec 1;98(22):2404-14 DCM





Mina K. Chung, MD *Circulation.* 1997;95:2517 (healed MI)



Fatal arrhythmias in human HF

Initiated by a nonreentrant mechanism (DAD or EAD)

- majority of human nonischemic CM

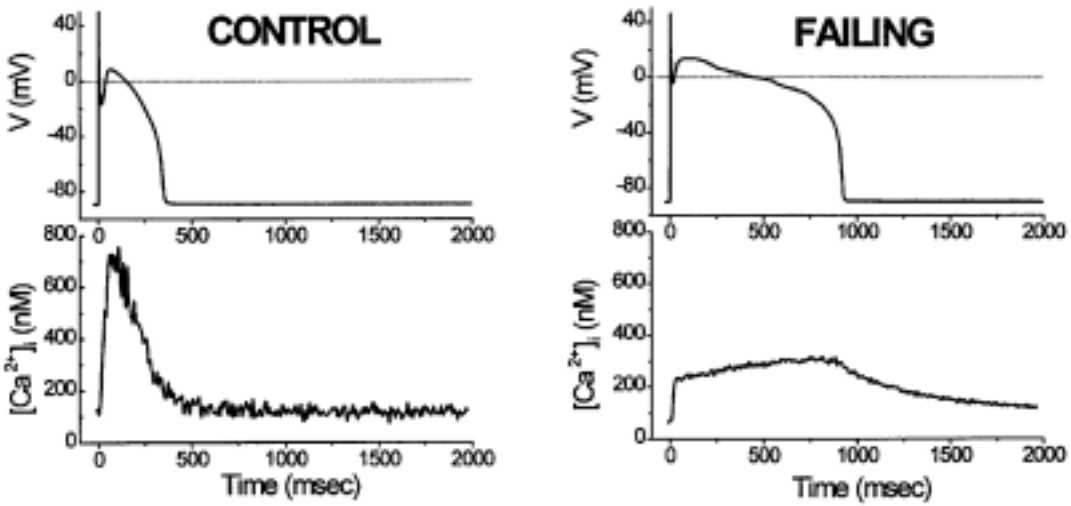
- half of human ischemic CM

1. Circulation. 1998 Dec 1;98(22):2404-14 DCM
2. Circulation. 1997 Jun 3;95(11):2528-40. healed MI

In Heart failure…

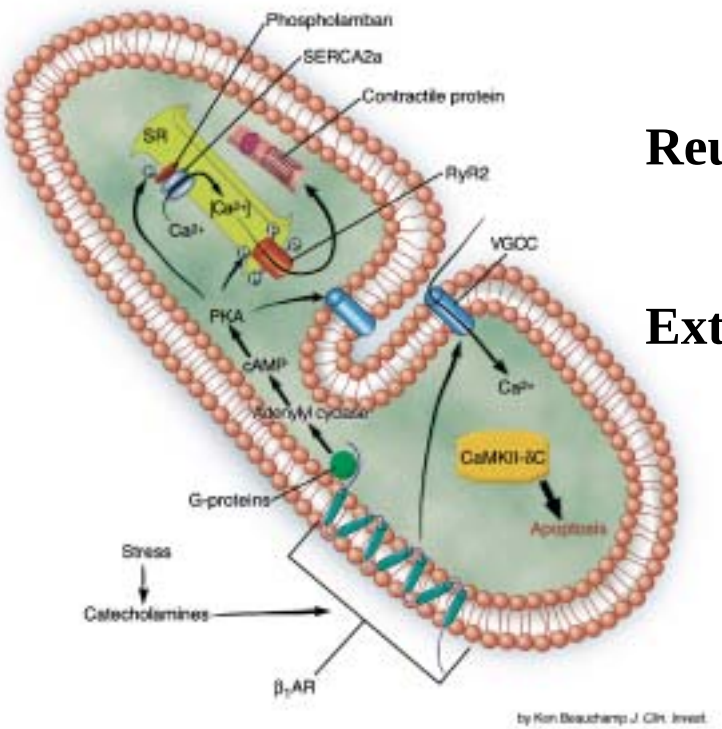
Membrane ion channel : AP prolongation

Sarcoplasmic reticulum : defective Ca handling



Gordon F. Tomaselli , Eduardo Marban
Cardiovascular Research 42 (1999) 270–283

Calcium handling: phyisology

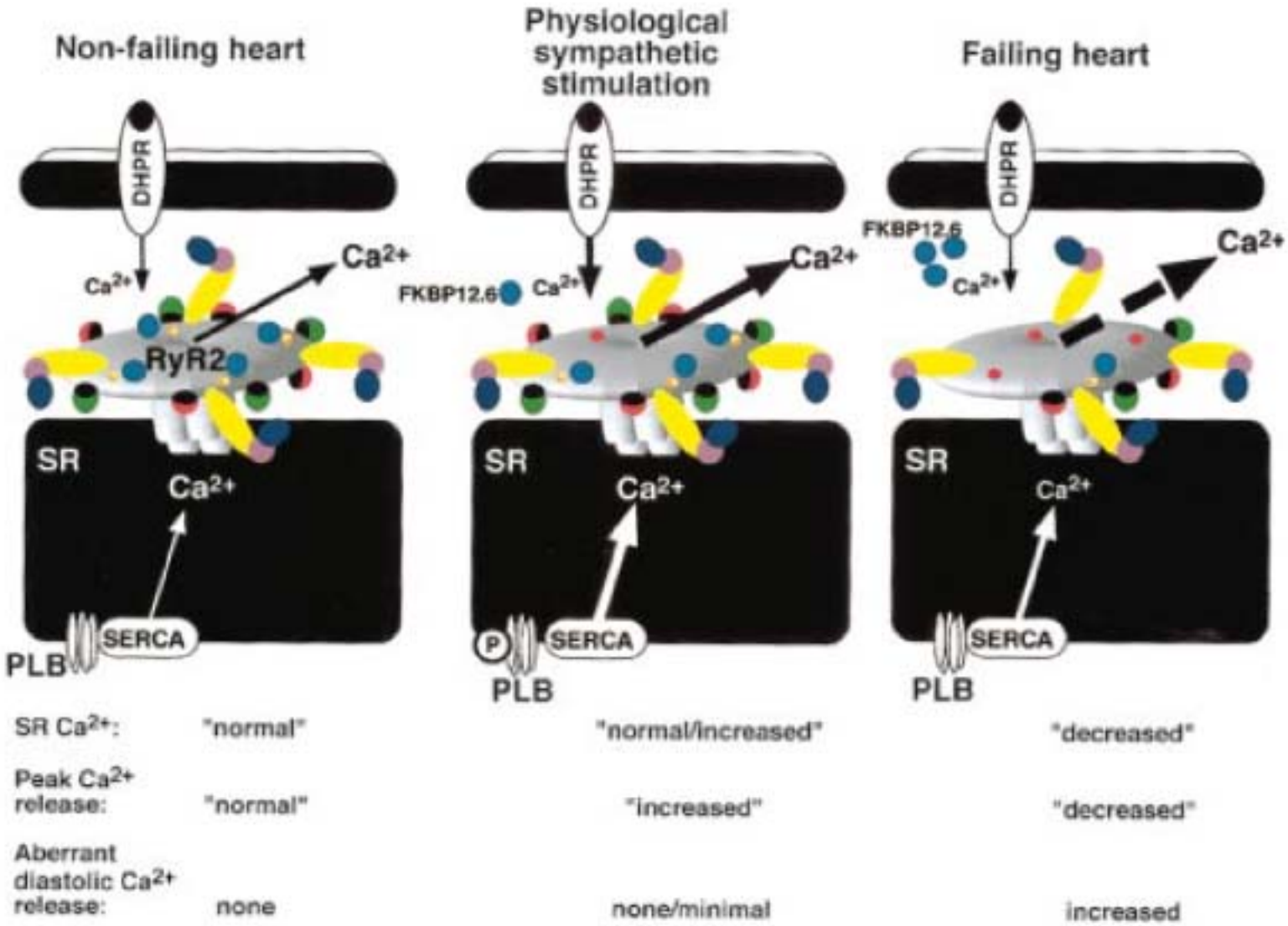


Trigger : I_{ca}

Release : Ca-induced Ca release

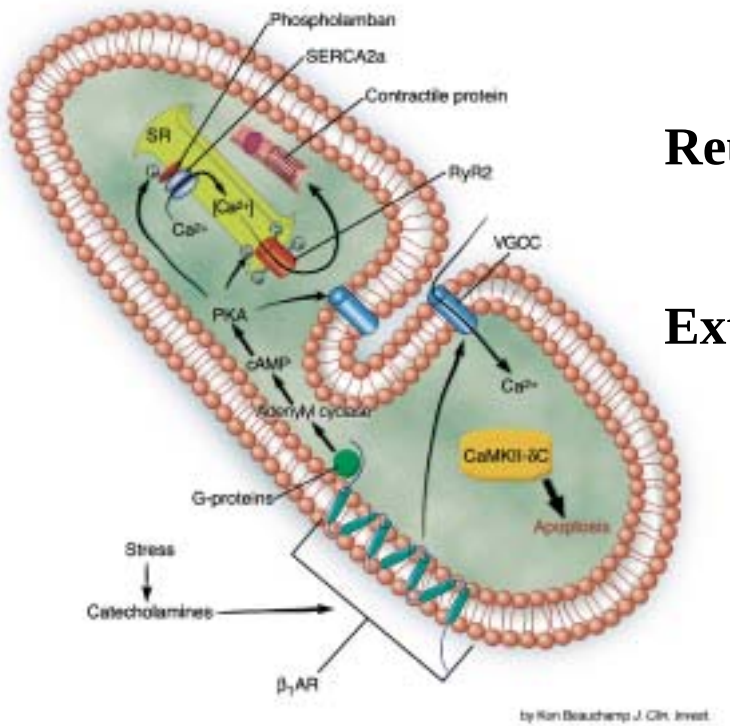
Reuptake : SERCA

Extrusion : NCX



Cardiac Intracellular Calcium Release Channels Role in Heart Failure
Andrew R. Marks Circ Res. 2000;87:8-11

Calcium handling: in CHF



Trigger : I_{ca}

Release : **Ca-induced Ca release**

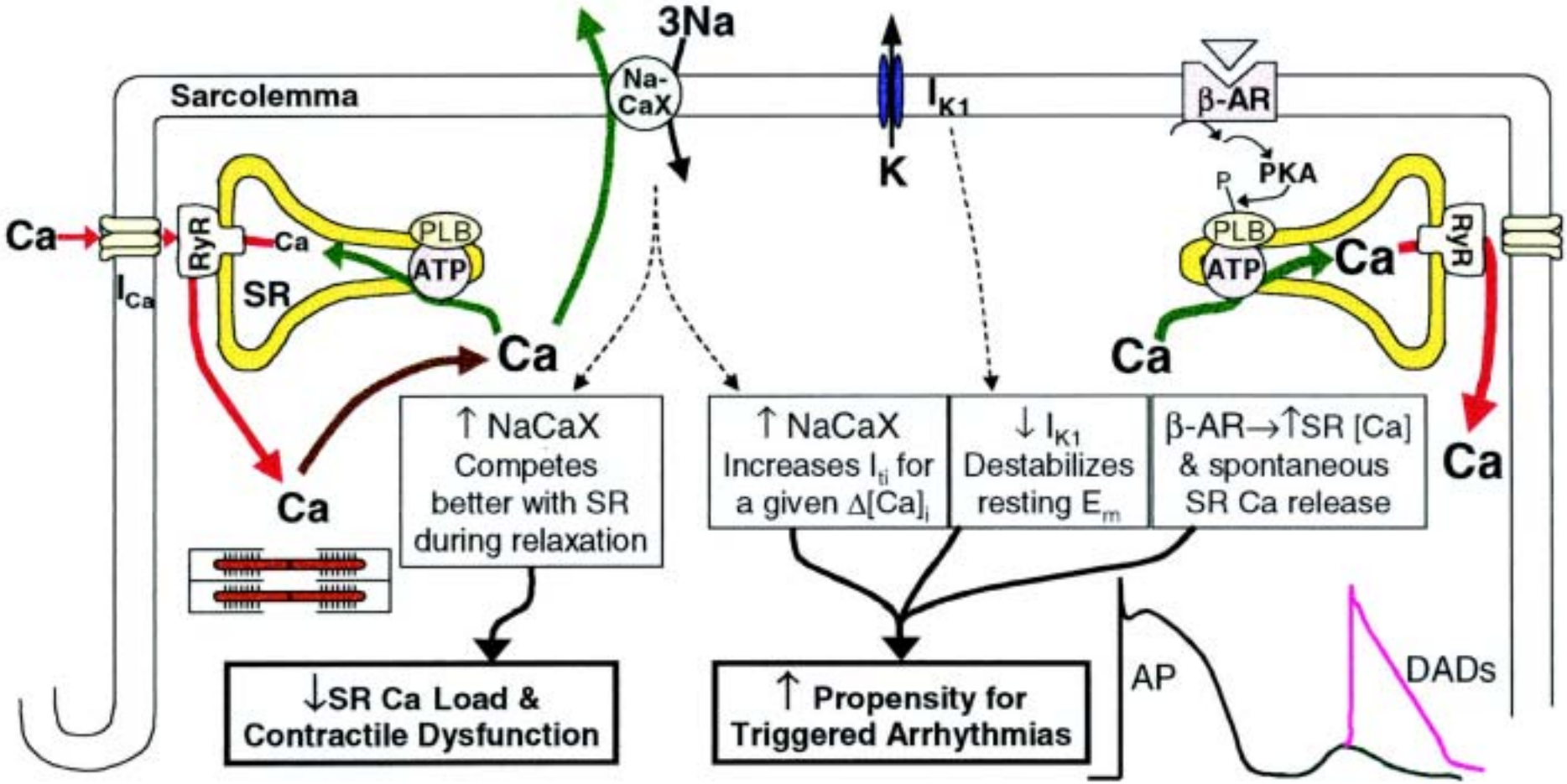
(hyperphosphorylation of RyR)

Reuptake : **SERCA**

(decreased SERCA)

Extrusion : **NCX**

(increased NCX)



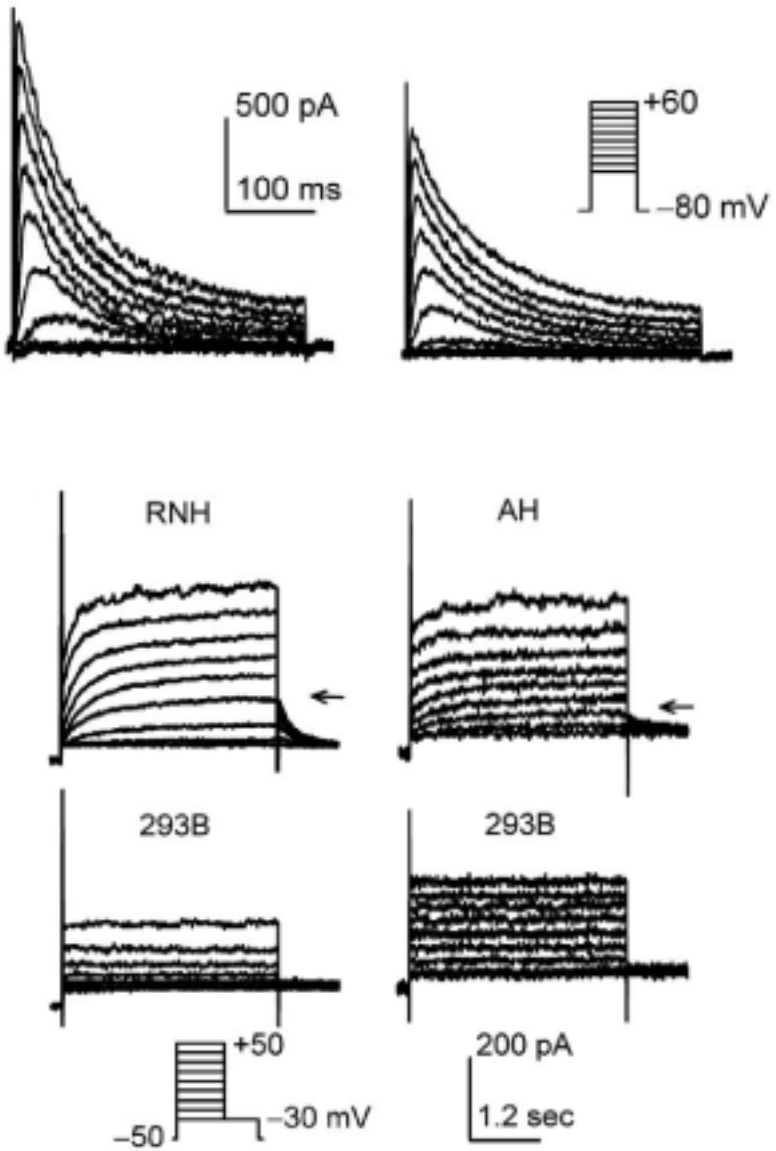
Steven M. Pogwizd, Circ Res. 2001;88:1159-1167

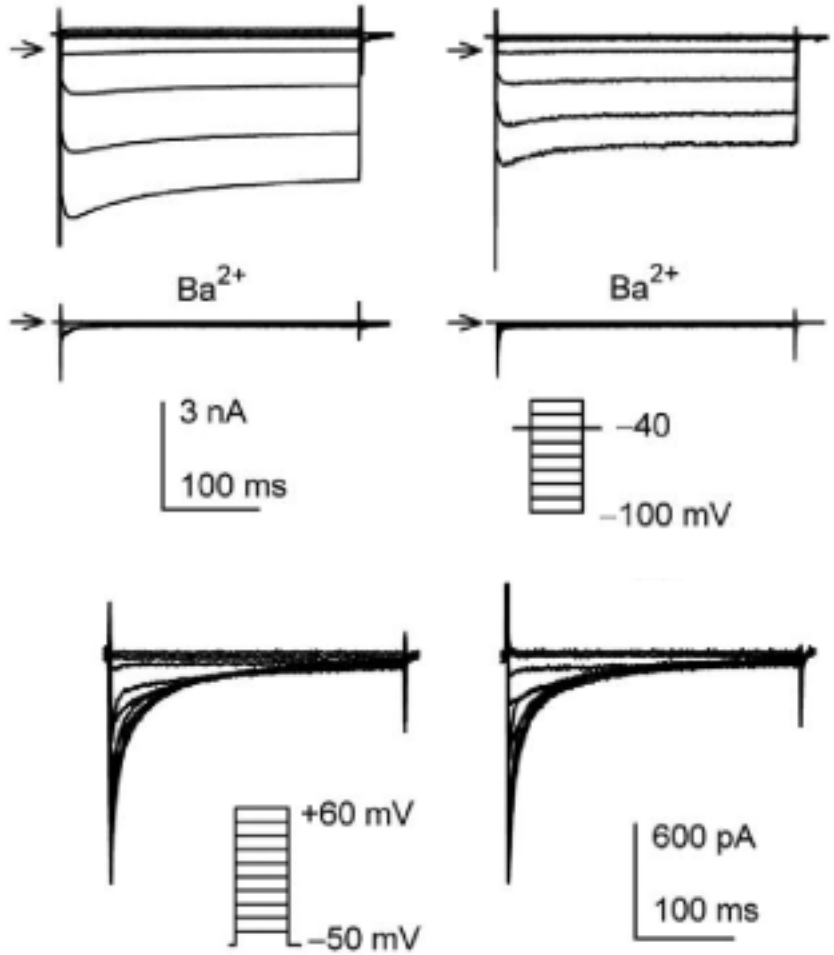
Reentry

- **anatomic (scar-related, BBR)**
- **functional**

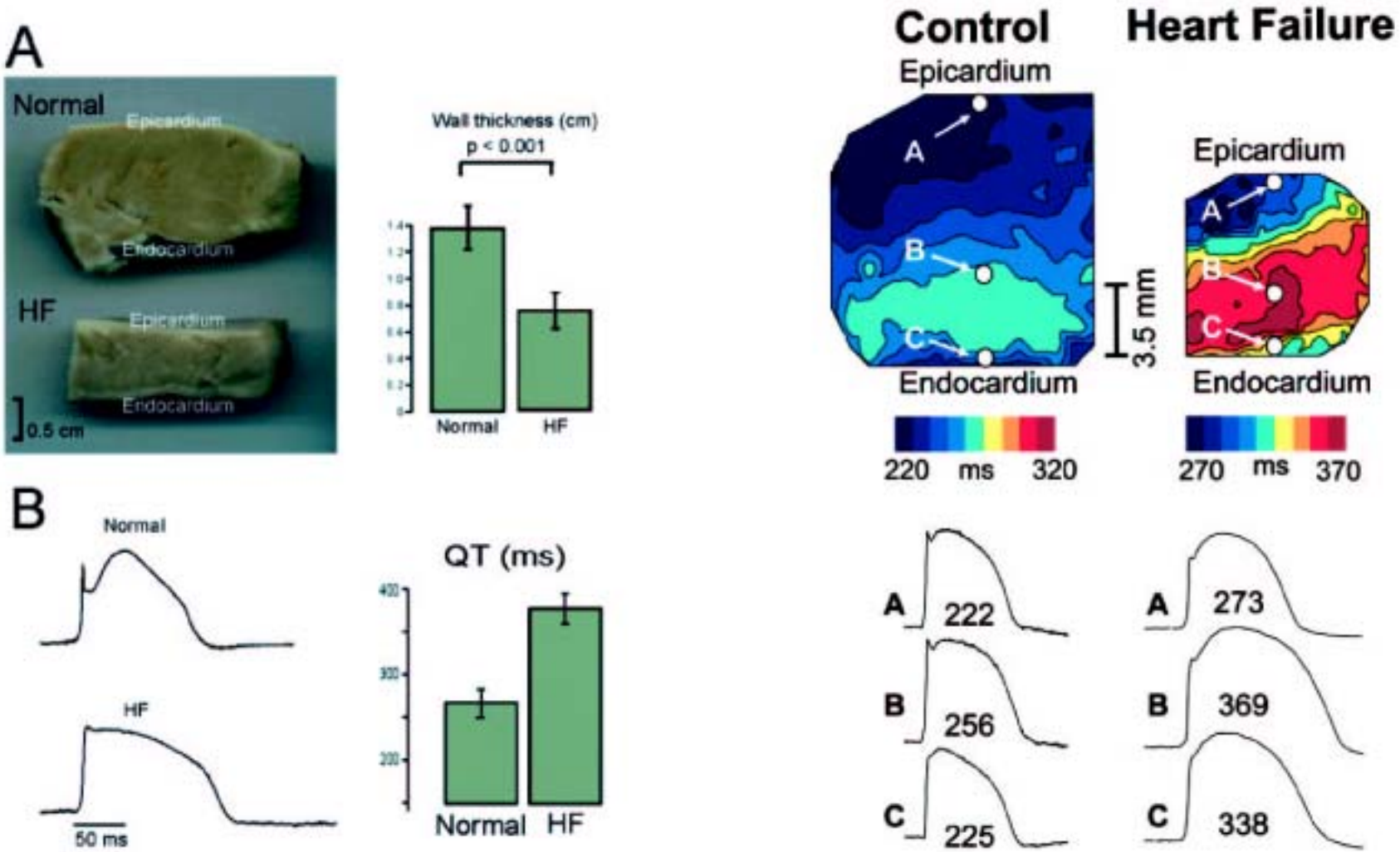
Focal

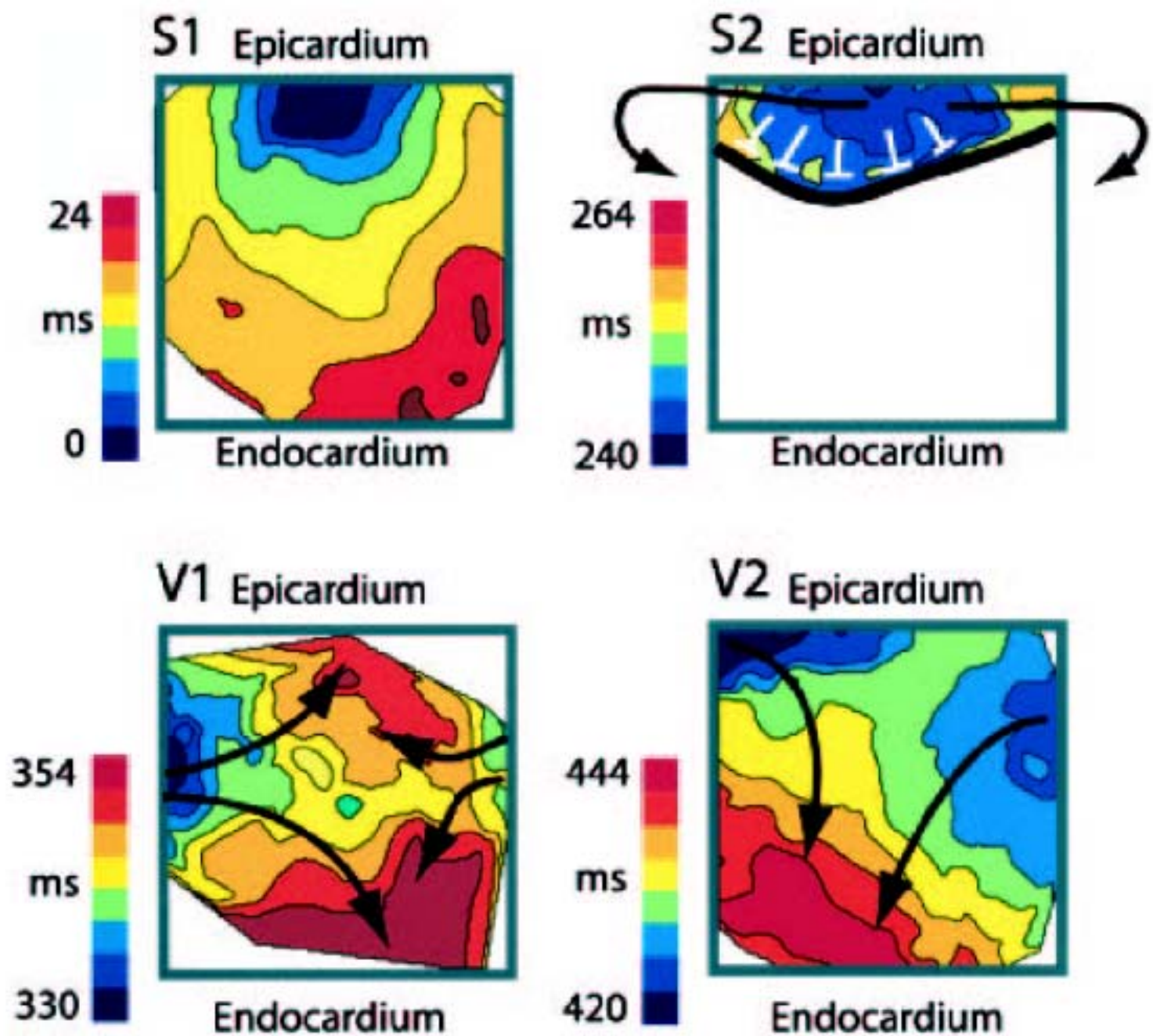
- **DAD** ← **altered Ca handling**
- **automatic**





Li GR, Lau CP, Leung TK, Nattel S.
Ionic current abnormalities associated with prolonged action potentials in cardiomyocytes from diseased human right ventricles.
Heart Rhythm. 2004 Oct;1(4):460-8.


A
Normal
Epicardium
Endocardium
HF
Epicardium
Endocardium
0.5 cm
Wall thickness (cm)
p < 0.001
Normal
HF
B
Normal
HF
50 ms
QT (ms)
Normal
HF
Control
Heart Failure
Epicardium
A
B
C
Endocardium
3.5 mm
220 ms 320
Epicardium
A
B
C
Endocardium
270 ms 370
A 222
B 256
C 225
A 273
B 369
C 338


S1 Epicardium
24
ms
0
Endocardium
S2 Epicardium
264
ms
240
Endocardium
V1 Epicardium
354
ms
330
Endocardium
V2 Epicardium
444
ms
420
Endocardium

Reentry

- **anatomic (scar-related, BBR)**
- **functional** ← **K channel remodeling**

Focal

- **DAD**
- **automatic**

Sustained monomorphic ventricular tachycardia in nonischemic heart disease

26 consecutive pts with nonischemic CM with recurrent VT

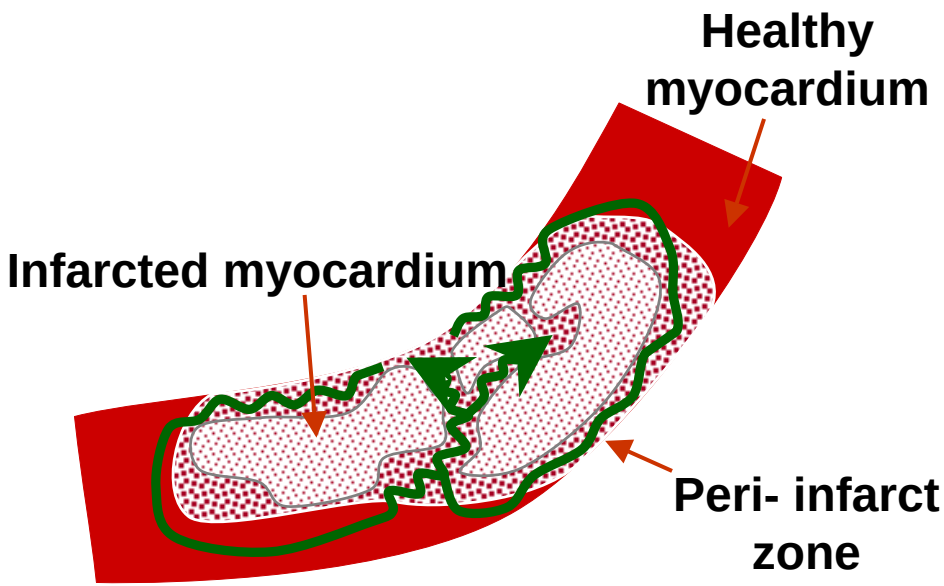
- 16/26 (62%), scar-related, reentrant mechanism.

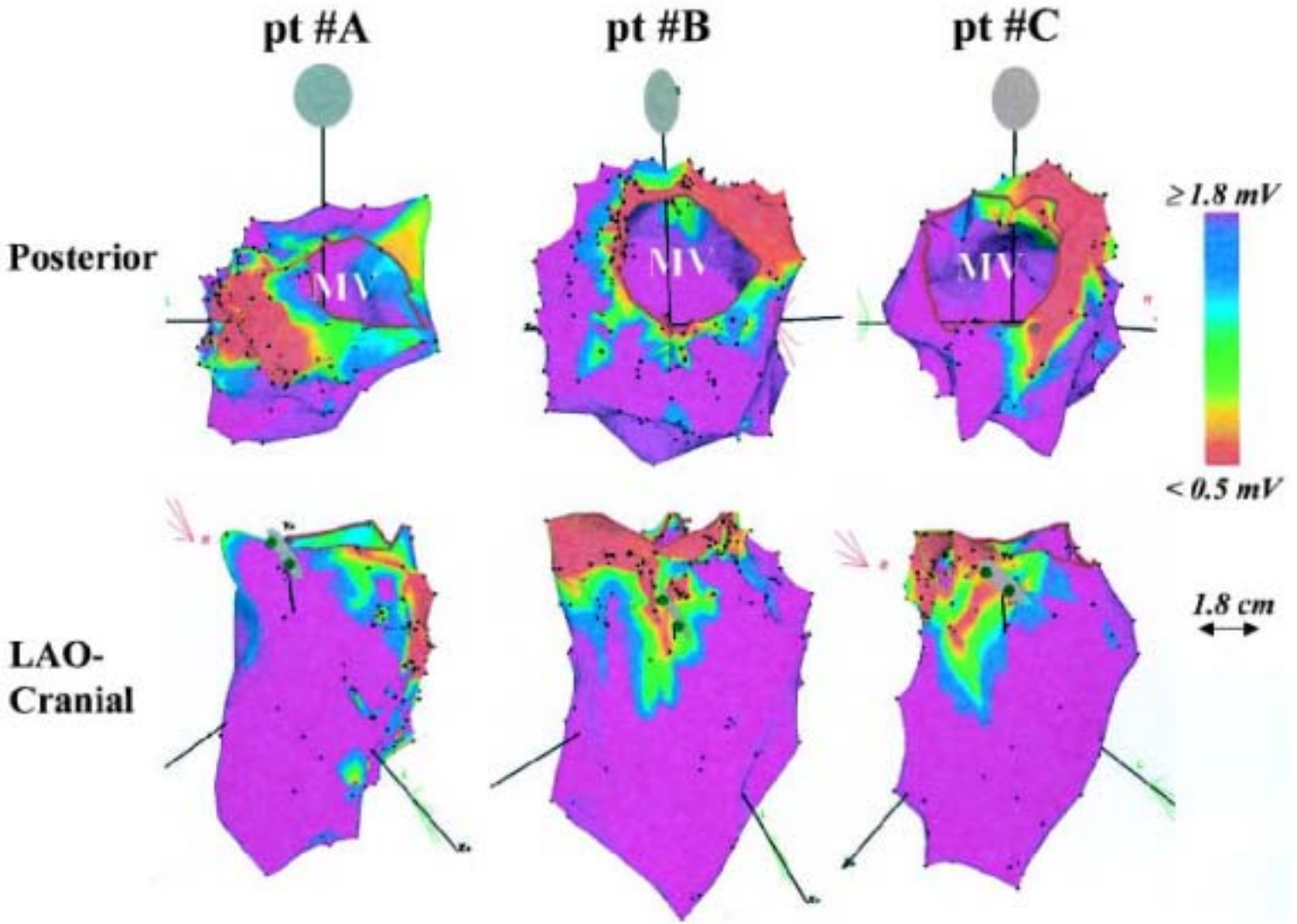
- 5/26 (19%), bundle branch or interfascicular reentry

- 7/26 (27%), focal automaticity (4/7: tachycardiomyopathy)

J Cardiovasc Electrophysiol. 2000 Jan;11(1):11-7.

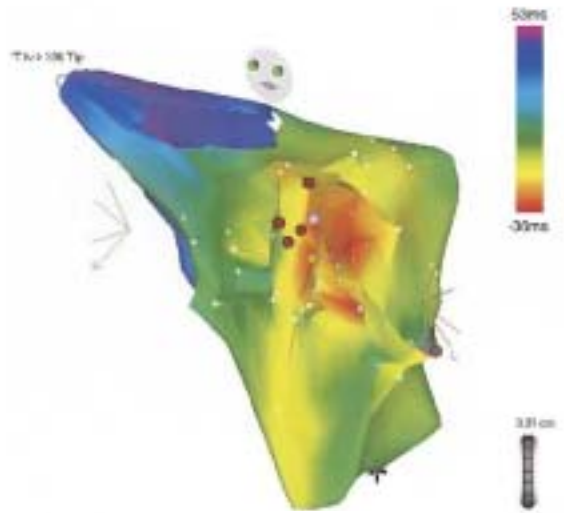
Ventricular Tachycardia in Healed Myocardial Infarction



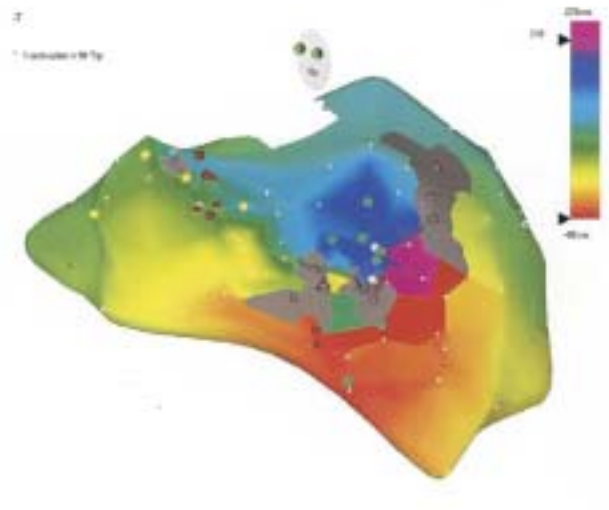


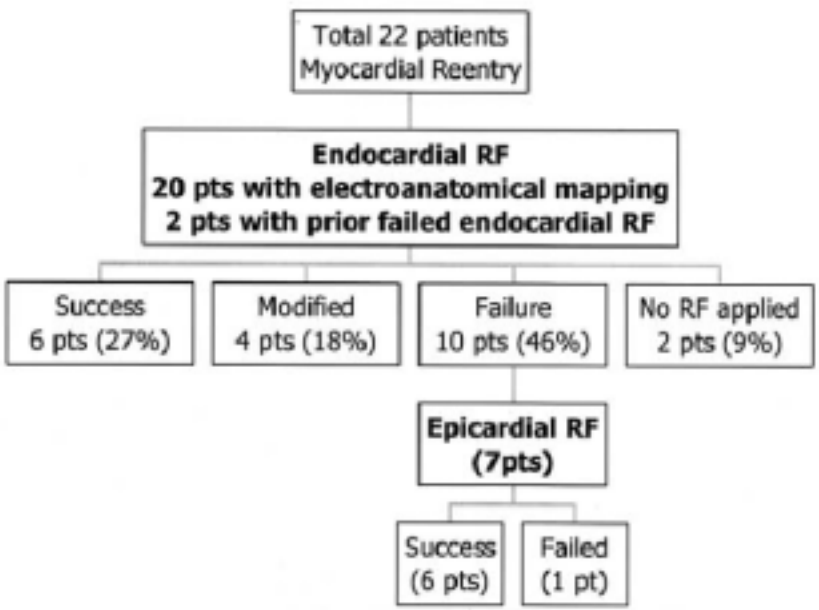
Francis E. Marchlinski *Circulation*. 2003;108:704-710

A)

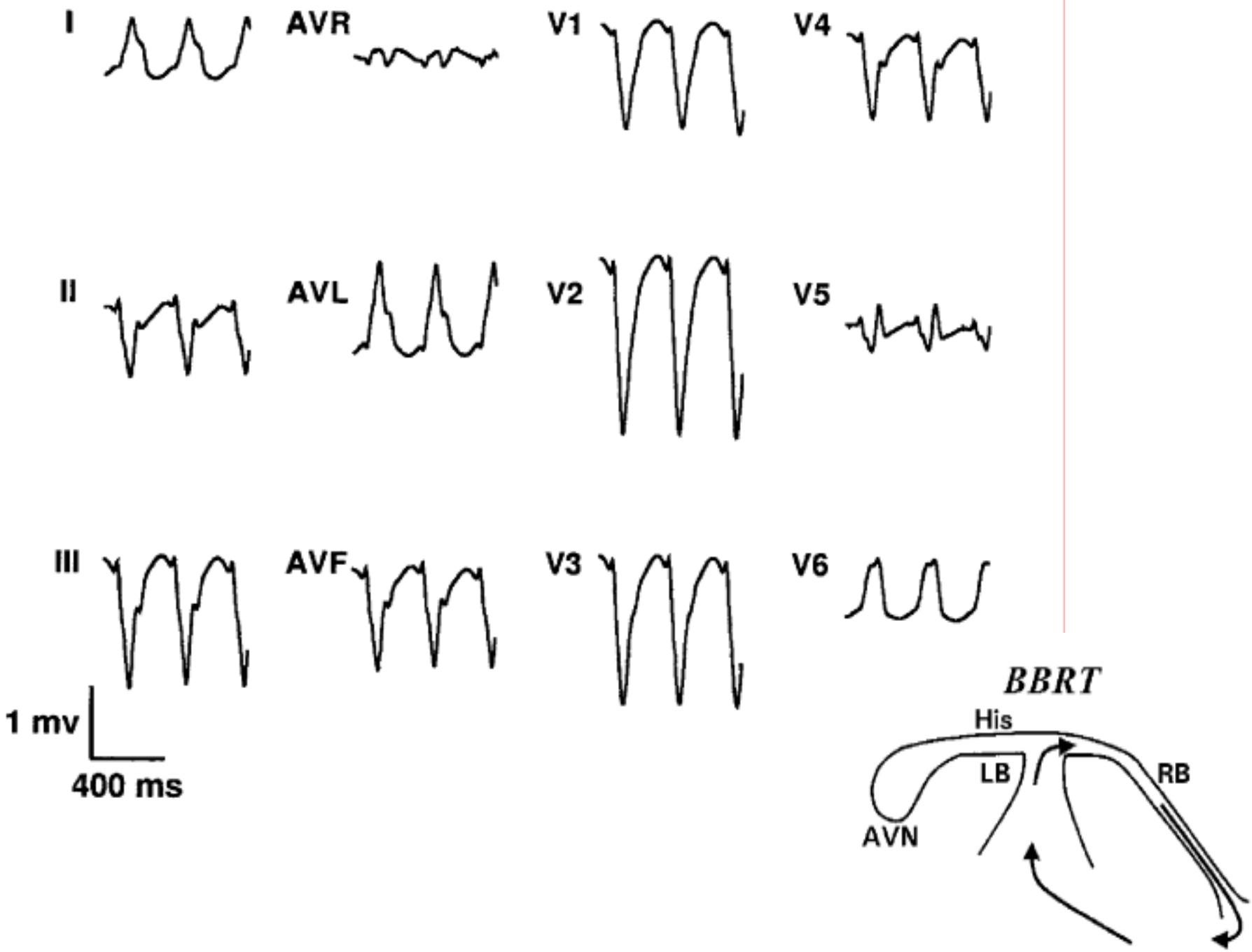


B)





Kyoko Soejima J Am Coll Cardiol 2004;43:1834–42


I
AVR
V1
V4
II
AVL
V2
V5
III
AVF
V3
V6
1 mv
400 ms
BBRT
His
LB
RB
AVN

Reentry

- **anatomic (scar-related, BBR)**
- **functional**

Focal

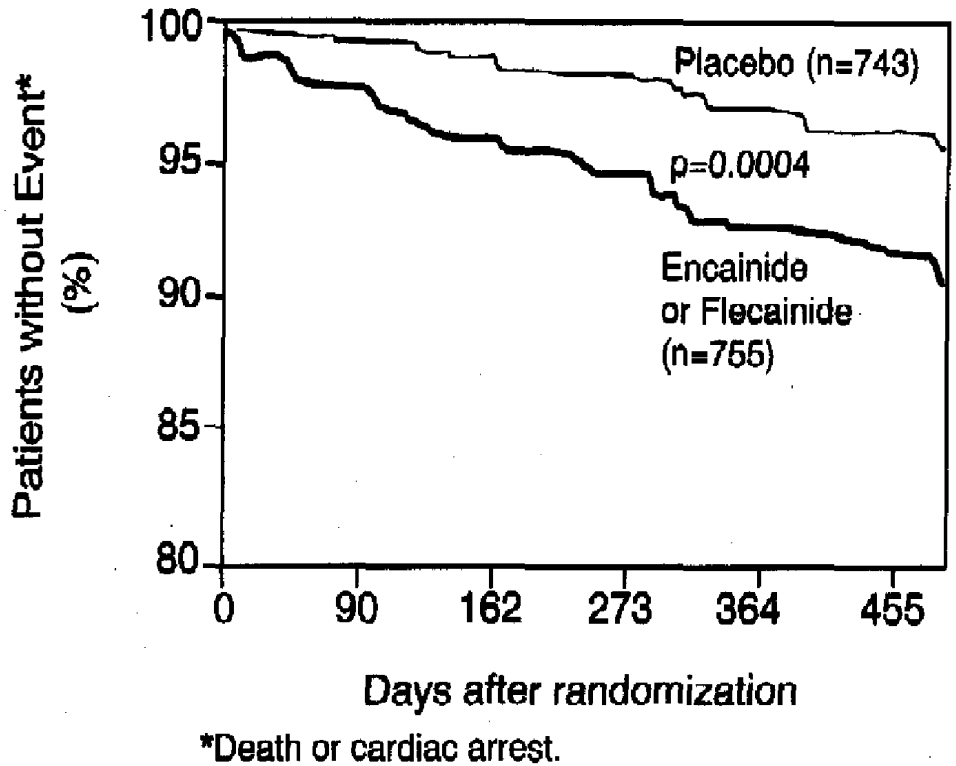
- **DAD**
- **automatic**

Antiarrhythmic drug therapy

Vaughan-Williams classification

Class I	-	quinidine, procainamide
	-	lidocaine, mexiletine
	-	propafenone, flecainide
Class II	-	propranolol
Class III	-	sotalol, amiodarone
Class IV	-	verapamil

Cardiac Arrhythmia Suppression Trial : *CAST*



VPD

↓

SCD, mortality

NEJM 1989;321:406

ESVEM *Eelectrophysiologic study vs Electro- cardiographic monitoring*

VT, cardiac arrest, syncope
HM > 9 PVCs/hr, EPS inducibility

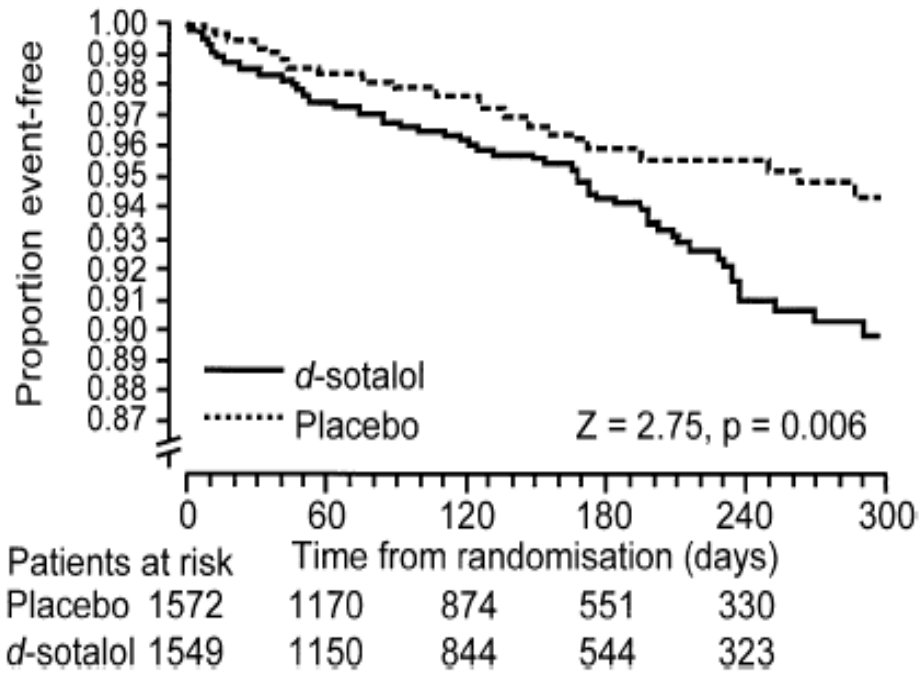
Sotalol was superior *to class I agents wtih respect to arrhythmia recurrence, arrhythmia mortality, cardiac mortality, or all-cause mortality.*

CASCADE *Cardiac Arrest in Seattle : Conventional vs Amiodarone Drug Evaluation*

survivors of out-of-hospital VF
(most had CAD with prior MI, half had CHF, mean EF 35%)
empiric amiodarone vs quinidine, procainamide, flecainide
Amiodarone : better survival
less likely to receive a shock from ICD

Survival with Oral d-Sotalol (SWORD)

1549 patients with LVEF < 41%
Recent(6-42d)MI, or remote (>42)MI with CHF
Randomization: d-Sotalol vs placebo
Mortality: d-Sotalol vs placebo(5.0 vs 3.1%)



d,l-Sotalol

d,l-sotalol (cf. d-sotalol) : nonspecific beta-blocker without ISA
(significant BB activity at >160mg/d)

T1/2 = 10-15hr

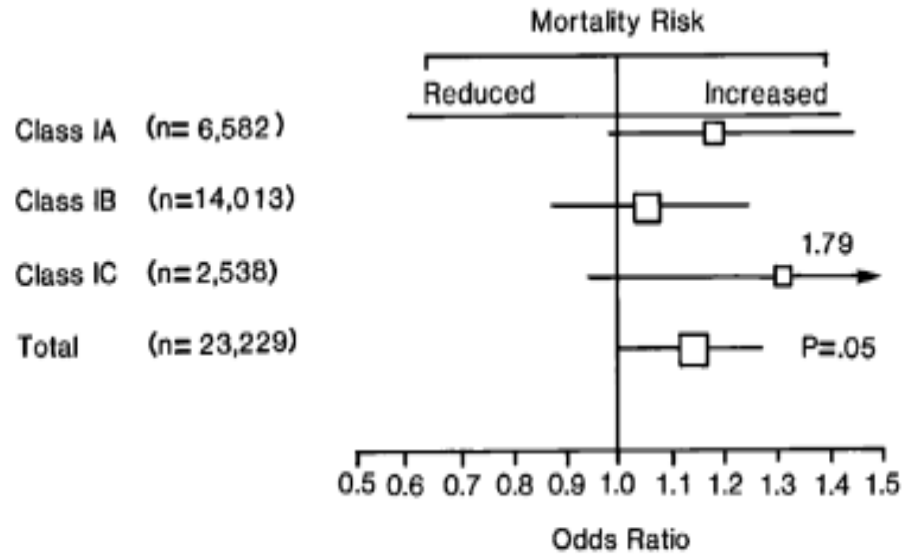
dosage : 80-160 mg bid

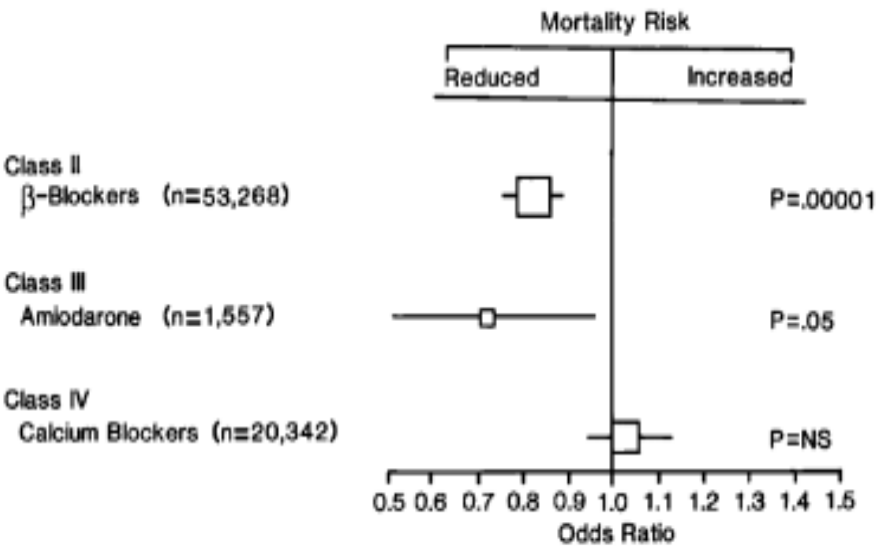
Study by Julian : total mortality 7.3 (sotalol) vs 8.9 % (control)
reduction in MI (5.7 vs 3.3 %)

Indication : AF in CAD

SE : proarrhythmia(4%, TdP 2.5%)
check ECG 2-3 days after dose elevation
hypotension, bradycardia

Amiodarone


Mortality Risk
Reduced
Increased
Class IA (n= 6,582)
Class IB (n=14,013)
Class IC (n=2,538)
Total (n= 23,229)
1.79
P=.05
0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Odds Ratio


Mortality Risk
Reduced
Increased
Class II
β-Blockers (n=53,268)
P=.00001
Class III
Amiodarone (n=1,557)
P=.05
Class IV
Calcium Blockers (n=20,342)
P=NS
0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Odds Ratio

Dofetilide

I_{Kr} blocker

DIAMOND : D-MI (<35%+MI), D-CHF (<35%+CHF)
placebo controlled design
no difference in mortality, arrhythmic death
Indication : AF in CAD
SE : proarrhythmia (TdP 3.3 -0.9 %)

New AADs currently in Clinical Trials

Amio-aqueous

Dronedarone : multiple K channel

Azimilide : multiple K channel

Tedisamil : multiple K channel

RSD1235 : atrial-selective

	Total Mortality	Sudden Death
ACE Inhibitors	++	+/-
β-Blockers	+++	++
Amiodarone	+/–	+/-
ICDs	++	+++
Antiarrhythmic Drugs	-	-