Clinical and Structural Aspects of Ventricular Tachycardia

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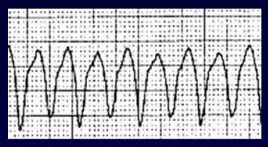
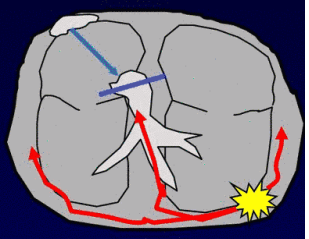
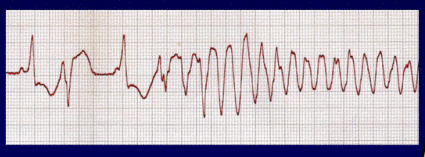
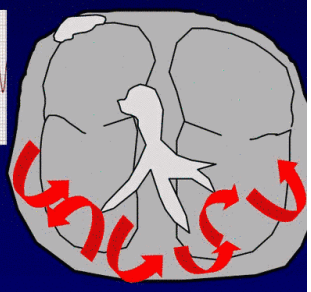
Ventricular Tachycardias

- Monomorphic
  - Scar – related reentry
  - Purkinje system
    - Focal - ?automatic
    - Bundle branch reentry
  - Idiopathic
- Polymorphic
  - Ischemia
  - Hypertrophy/Failure
  - acquired long QT syndrome
  - genetic syndromes
    - Long QT
    - Brugada
    - Short QT
    - Familial catecholaminergic PMVT

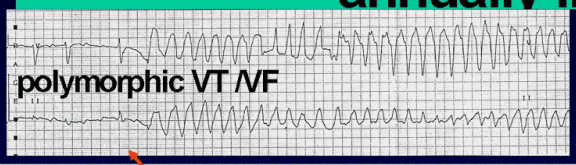


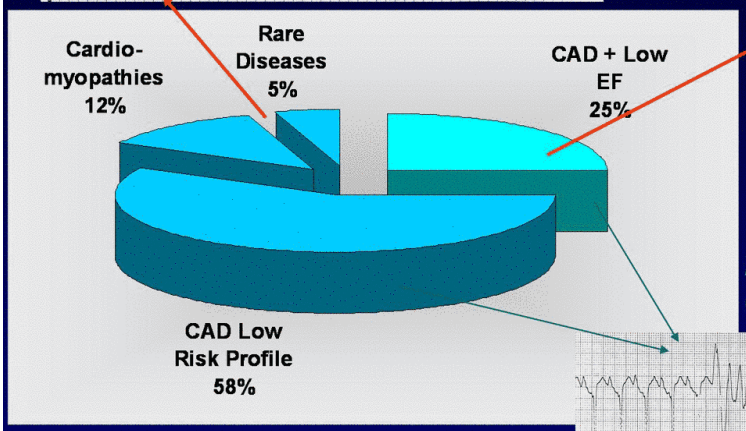




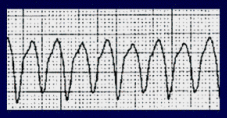


Sudden Death 150,000 – 300,000 annually in the US

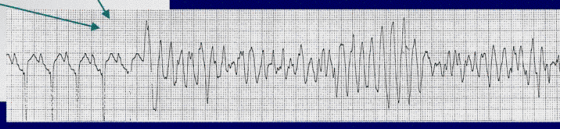




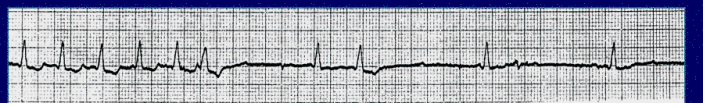
scar – related monomorphic VT



Acute infarction / ischemia causing polymorphic VT /VF

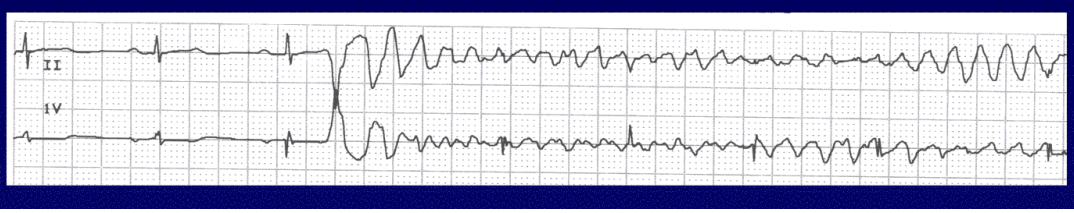


Sudden death with Bradycardia or pulseless electrical activity



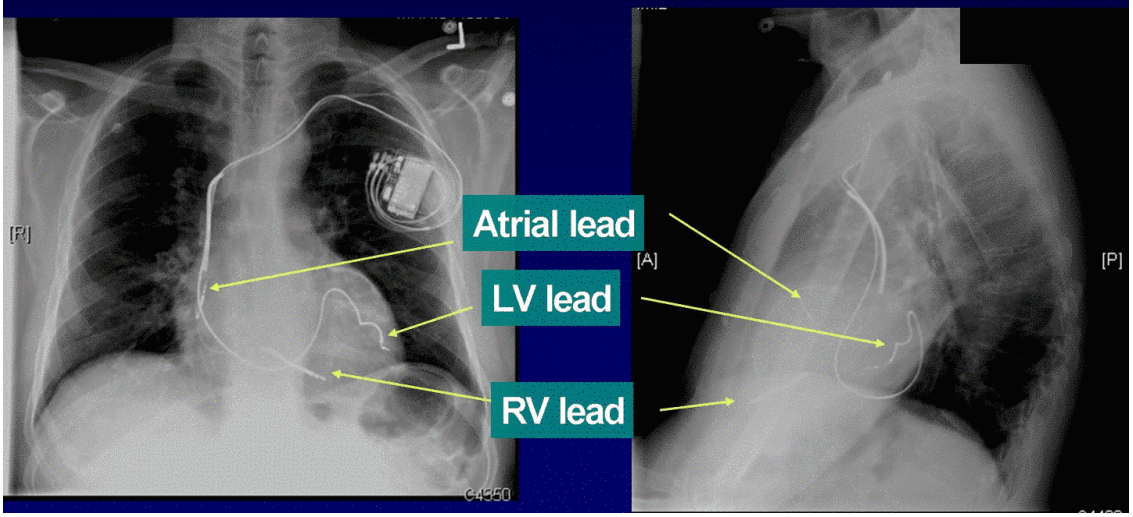
Polymorphic VT / VF due to Acute Myocardial Infarction

- Usually one episode early
- Associated with:
  - Larger infarcts
  - Genetic predisposition
  - Older age
- Survivors are not necessarily at increased risk for recurrent cardiac arrest

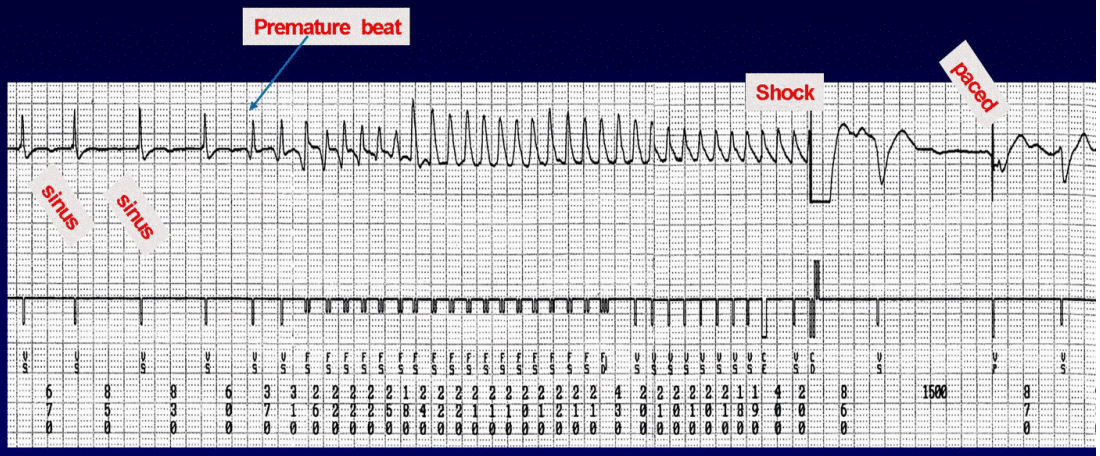


ICDs for patients at risk of sudden death

Secondary prevention: resuscitated from VT or VF
Primary prevention: high risk patients who have not yet had VT/VF

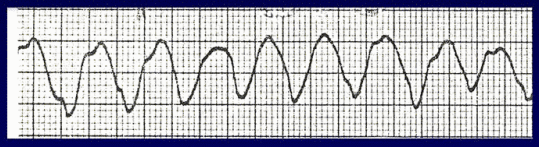


Spontaneous initiation of VT recorded from an ICD

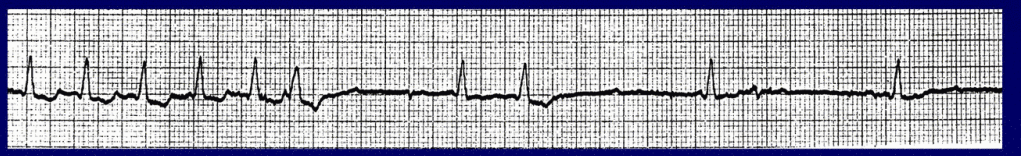


ICDs will not reverse all cardiac arrests

- acute myocardial infarction
- stroke
- hyperkalemia

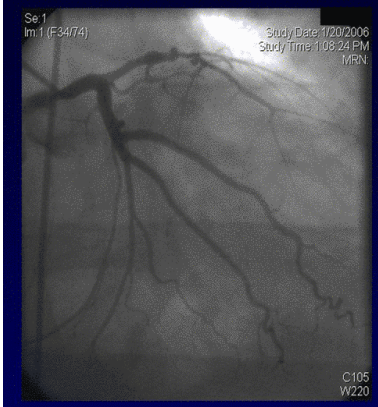


- pulmonary emboli



Case 1

- 59yo M
- 1984
  - Anterior MI → enrolled in SAVE
  - Relatively good health for 20 years
- January 2006
  - Presented with palpitations and wide QRS tachycardia
  - Failed IV amiodarone and adenosine → 50J shock
  - Multiple episodes of VT
  - Rx: captopril 50mg TID, ECASA 325mg, metoprolol 50mg BID, atorvastatin 40mg

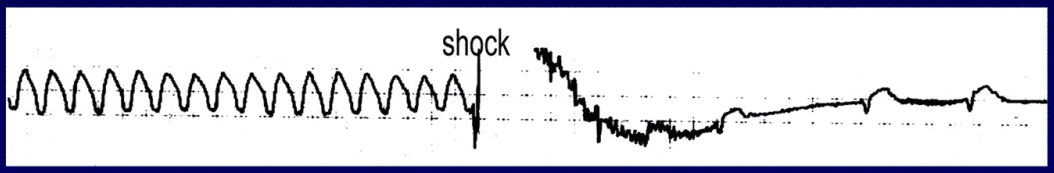


- Proximal LAD occlusion
- No revascularization indicated
- Poor LV function – LVEF 20%

A transplant story:

dilated heart failure, VT
ICD lead fracture - recurrent ICD shocks
rapid atrial fibrillation – recurrent ICD shocks

ICD explanted at the time of cardiac transplantation



Need for Arrhythmia Management After ICD placement

Primary Prevention ICD
shocks for VT - 5% year
Inappropriate shocks - 2.5%/yr
Need for AA drugs – 14%

Secondary Prevention ICD
shocks for VT: 40 – 60%
>3 shocks in 24 hrs: 20%
Need for AADs – 20%

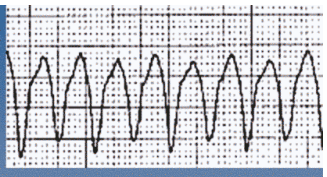
Symptomatic VT After ICD

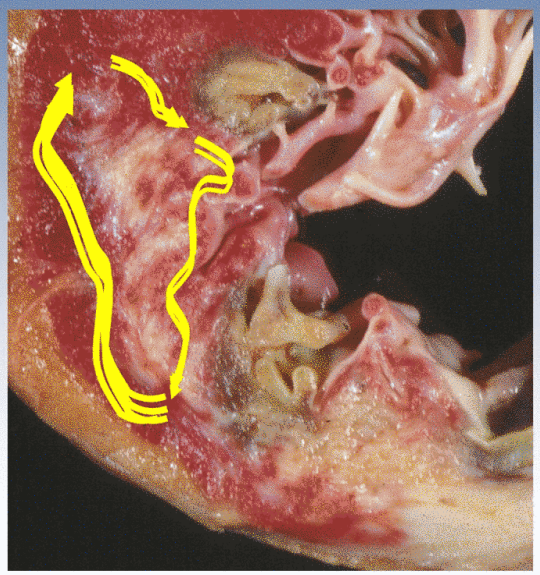
→ Antiarrhythmic Drugs

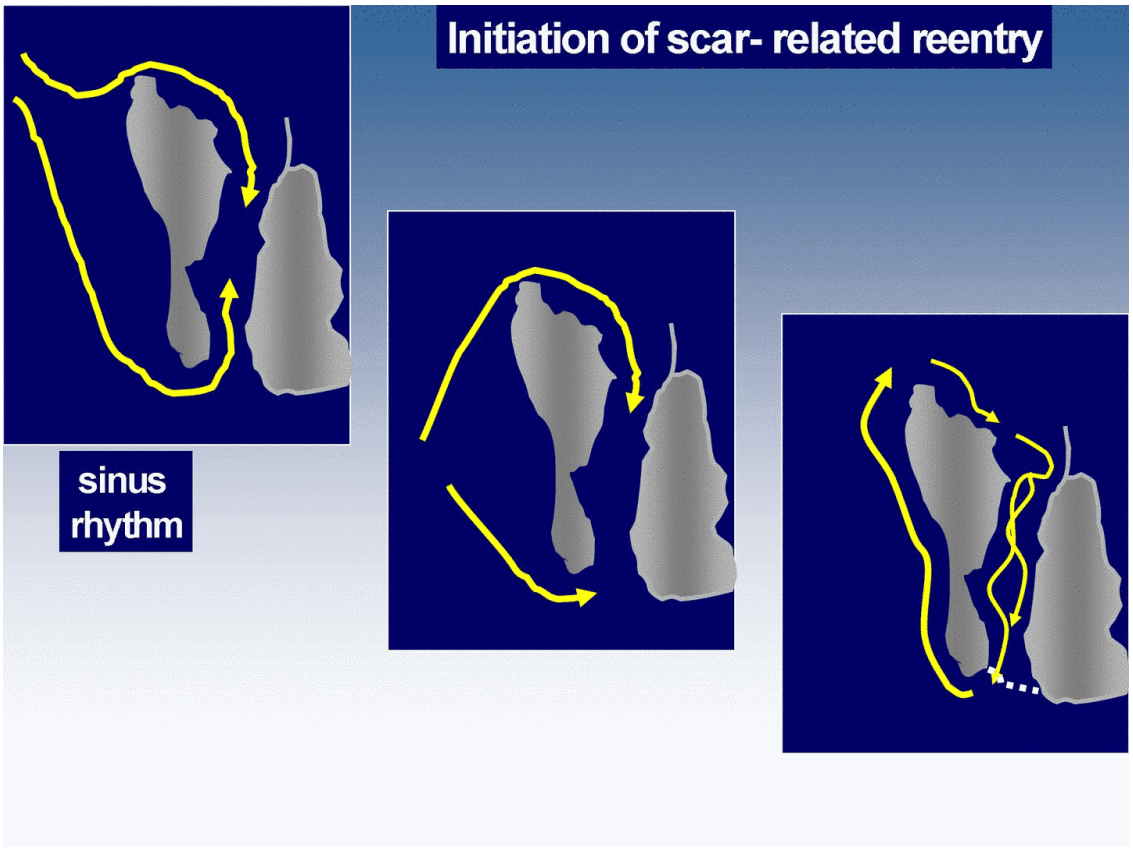
→ Catheter Ablation

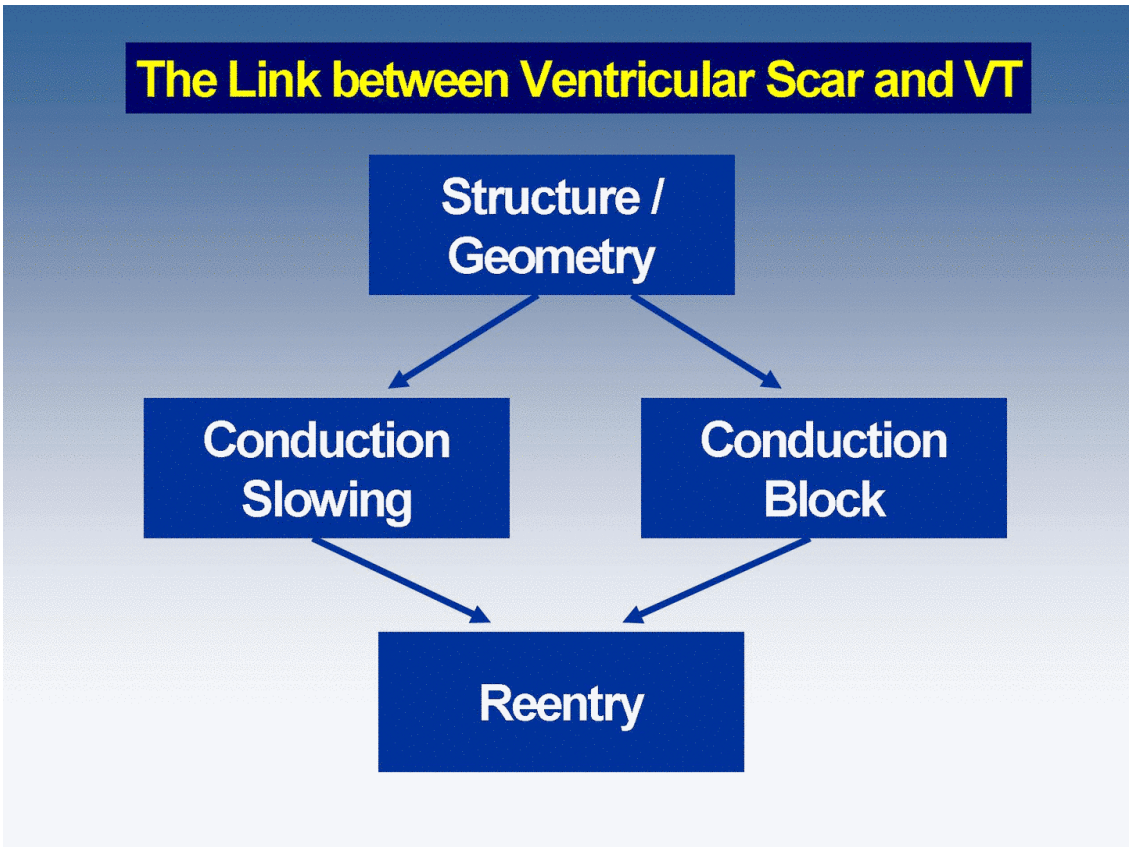
SCD-HeFT Bardy, G. H. et al. N Engl J Med 2005;352:225-237
MADIT II N Engl J Med 202;346:877
AVID VT storm, Exner et al Circ 2001;103:201
AVID Quality of life, Schron Circ 2002;105:589

Sustained Monomorphic VT: Reentry in an infarct scar



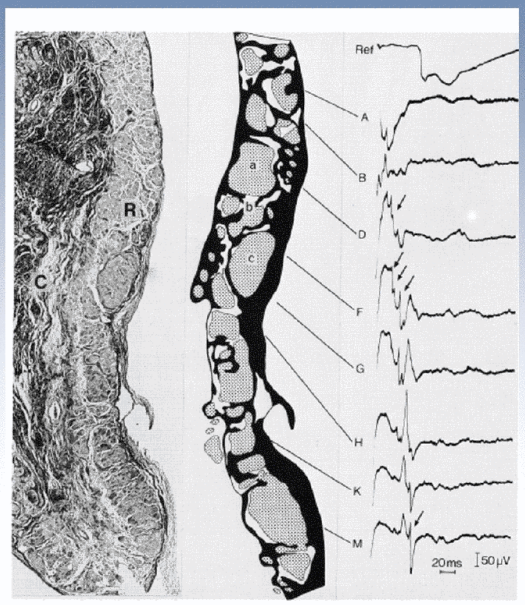



Initiation of scar- related reentry
sinus rhythm

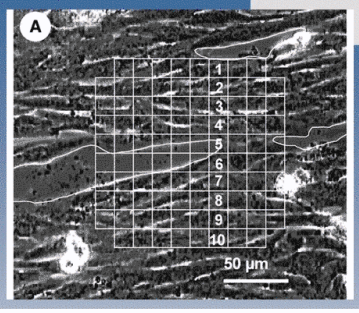

The Link between Ventricular Scar and VT
Structure / Geometry
Conduction Slowing
Conduction Block
Reentry

Reentry as a cause of VT in chronic ischemic heart disease
Zig – zag conduction causing slow conduction

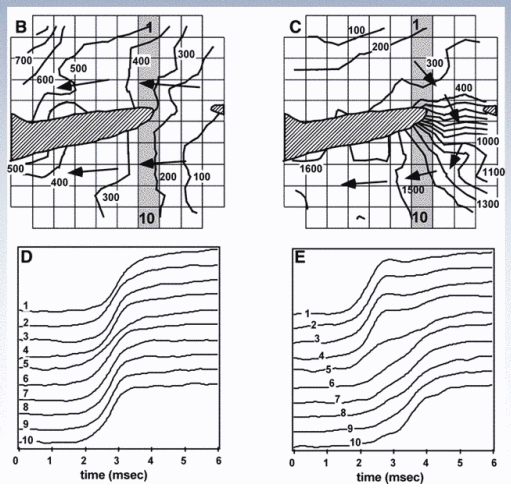
De Bakker, et al. Circulation 1988; 77:589. Circulation 1993;88:915.



Heterogeneity of propagation produced by anisotropic microscopic barriers



A: phase-contrast image of a cell culture (neonatal rat myocytes) with the overlaid diode array (30 μm per diode). Action potential upstrokes are measured at each diode location. The 2 clefts in the central area (outlined in white in *A* and marked by striations in *B* and *C*) form a narrow isthmus of 40 μm.

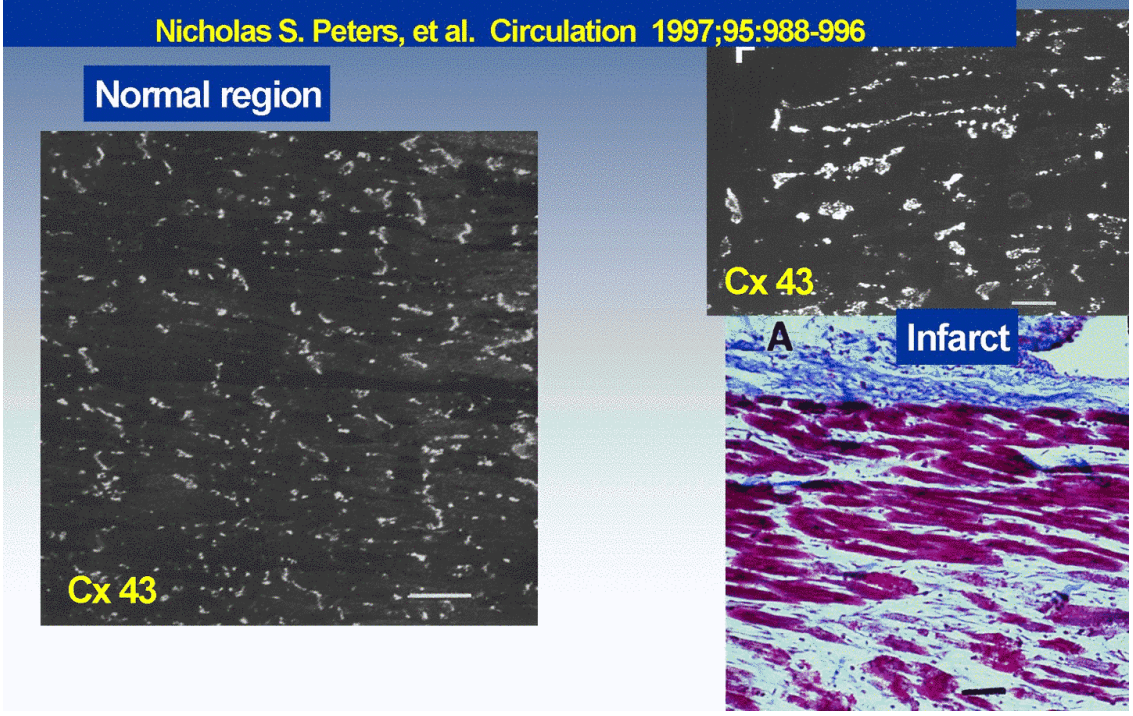


Action potential upstrokes during longitudinal and transverse conduction. Discontinuities in the action potential upstrokes and slowing of conduction occur at the expansion site during transverse propagation (*C* and *E*) while longitudinal propagation (*B* and *D*) is continuous.

KLEBER, A. G. et al. Physiol. Rev. 84: 431-488 2004;
from Fast et al Circ Res 79:115

Disturbed Connexin43 Gap Junction Distribution Correlates With Reentrant Circuits in the Epicardial Border Zone of Healing Canine Infarcts

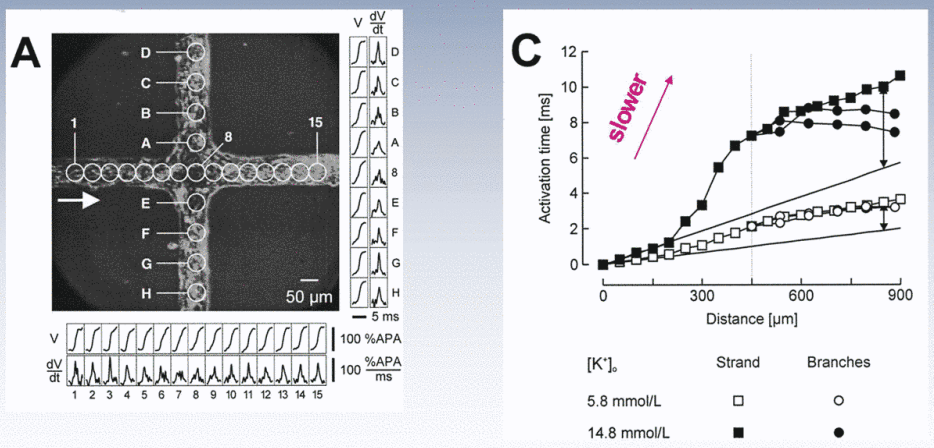
Nicholas S. Peters, et al. Circulation 1997;95:988-996



Slow Conduction in Cardiac Tissue, II Effects of Branching Tissue Geometry

Kucera et al. Circ Res 1998;83:795-805

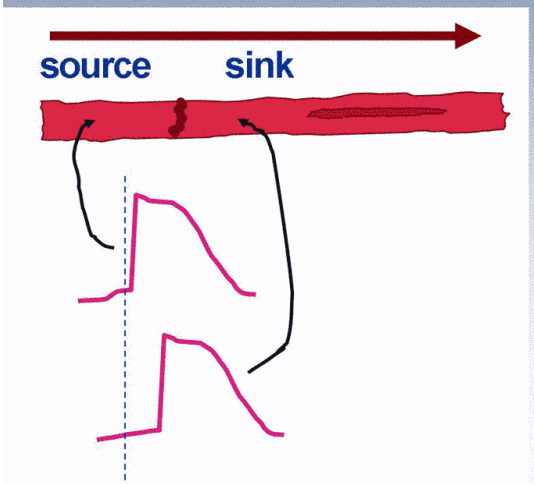
Conduction slowing at a branch point in cultured neonatal rat myocytes

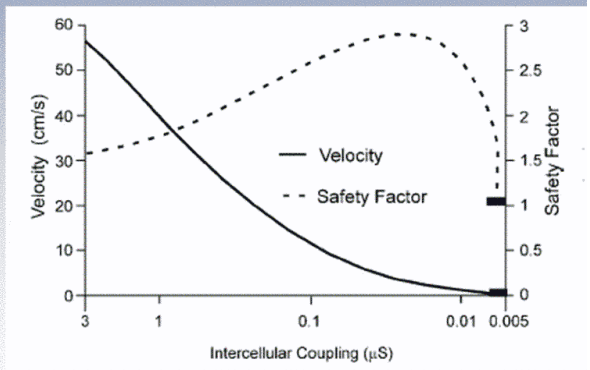


Decreased cell coupling creates slow but stable conduction:

less current is dissipated to surrounding cells

- the "Safety Factor" for conduction



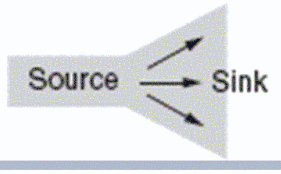


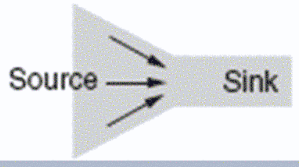
KLEBER, A. G. et al. Physiol. Rev. 84: 431-488 2004

Unidirectional conduction block due to source sink mismatch

small source large sink

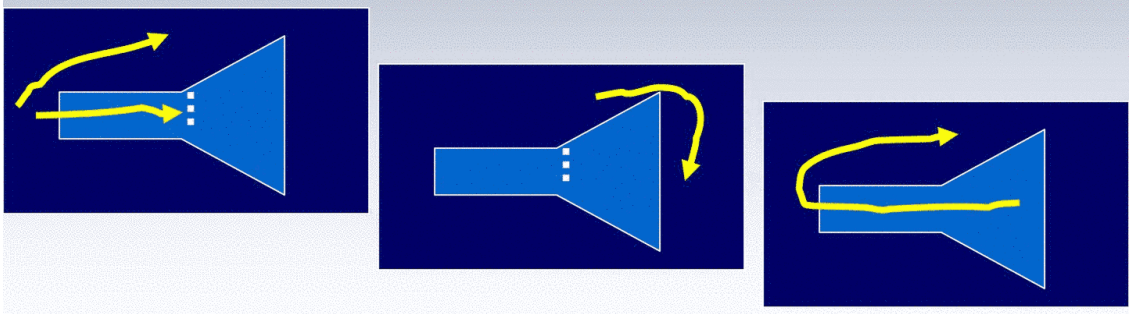
large source small sink





Risk of conduction block

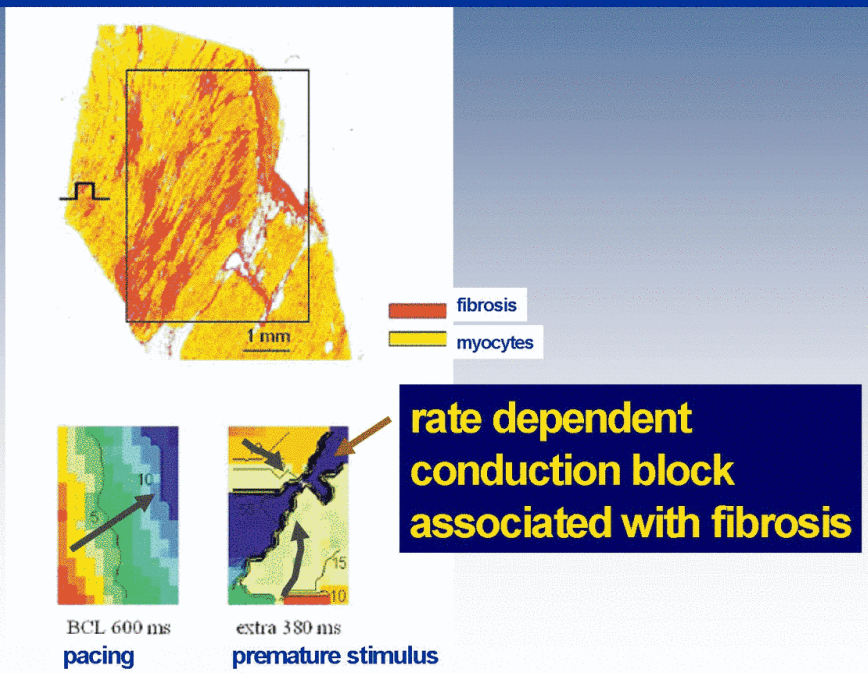
Stable conduction



Roden and Tomaselli. Conceptual basis for arrhythmology 2005

Three-dimensional anatomic structure as substrate for ventricular tachycardia/ventricular fibrillation

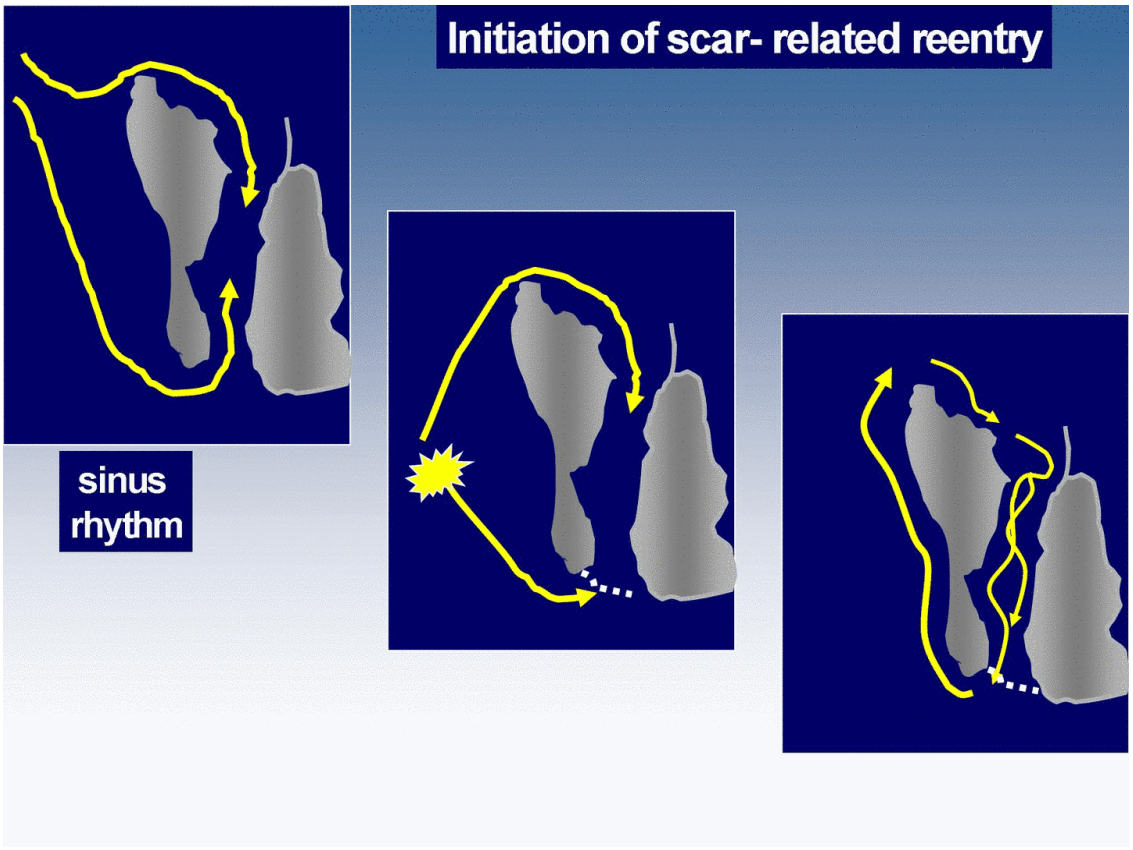
de Bakker, et al. Heart Rhythm 2005; 2:777

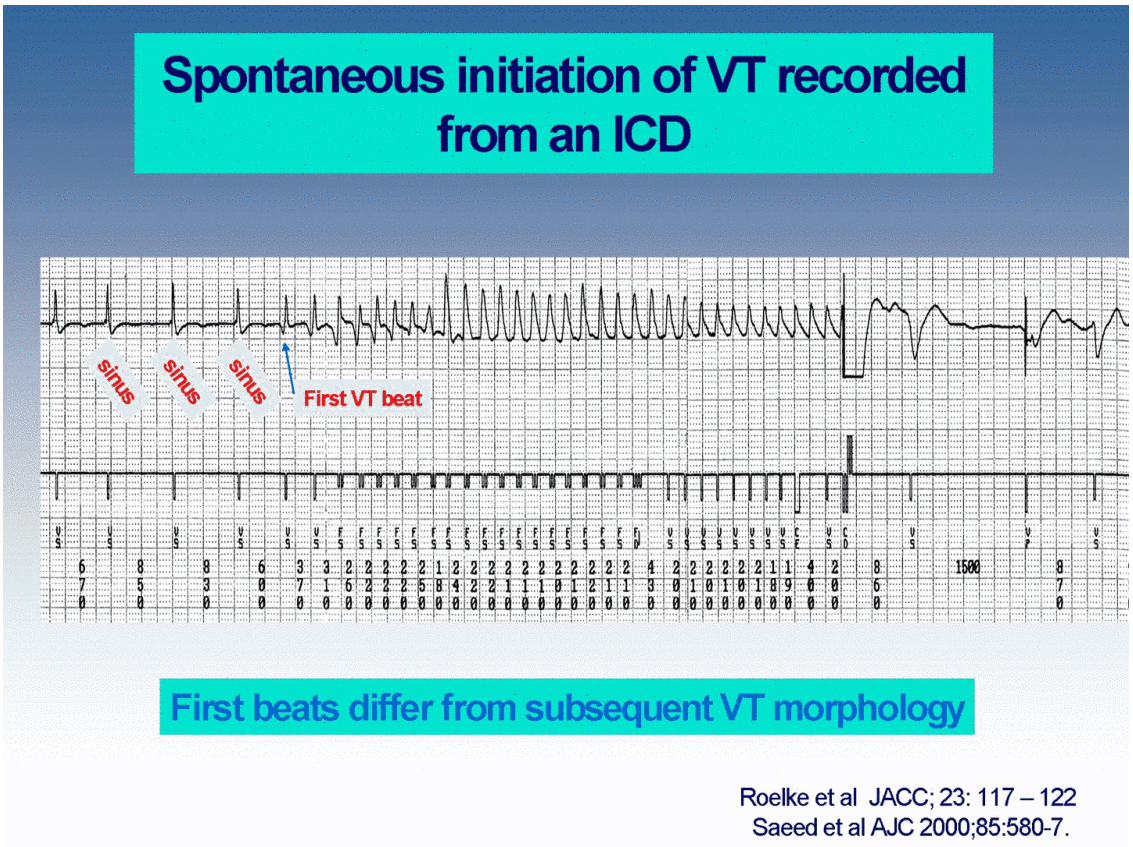


Remodeling in Cells From Different Regions of the Reentrant Circuit (Canine Infarct Model)

Baba, Boyden et al Circulation 2005; 112: 2386 - 2396.

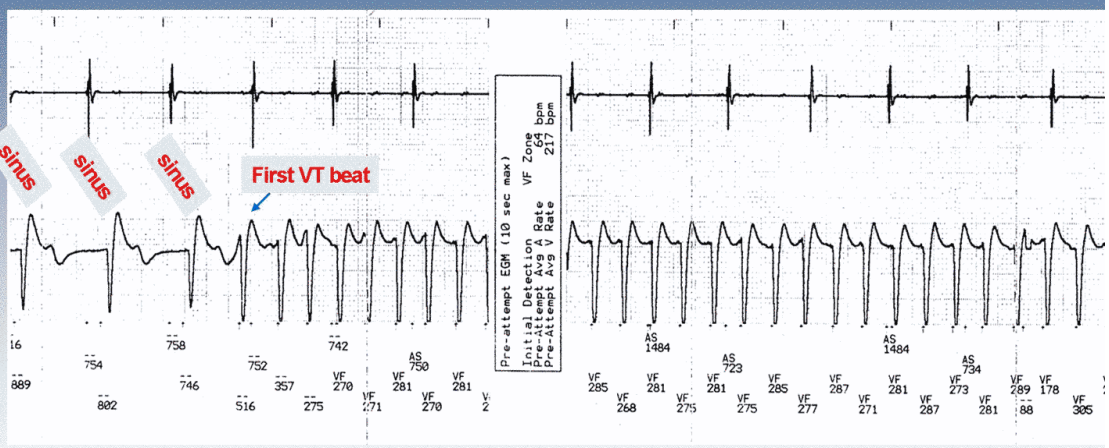
- /Na density was reduced in both IZc and IZo, and the kinetic properties of IZc /Na were markedly altered versus IZo.
- Structural remodeling of the sodium channel protein Nav1.5 occurred in IZs, with cell surface localization differing from normal cells.
- Both IZc and IZo have similar but reduced /CaL, whereas IZc showed changes in Ca2+ current kinetics with an acceleration of current decay.
- In computer simulations of the 2D EBZ incorporating both /Na and /CaL current differences stabilized the simulated reentrant circuit, and lines of block formed between the 2 distinct regions.





Roelke et al JACC; 23: 117 – 122
Saeed et al AJC 2000;85:580-7.

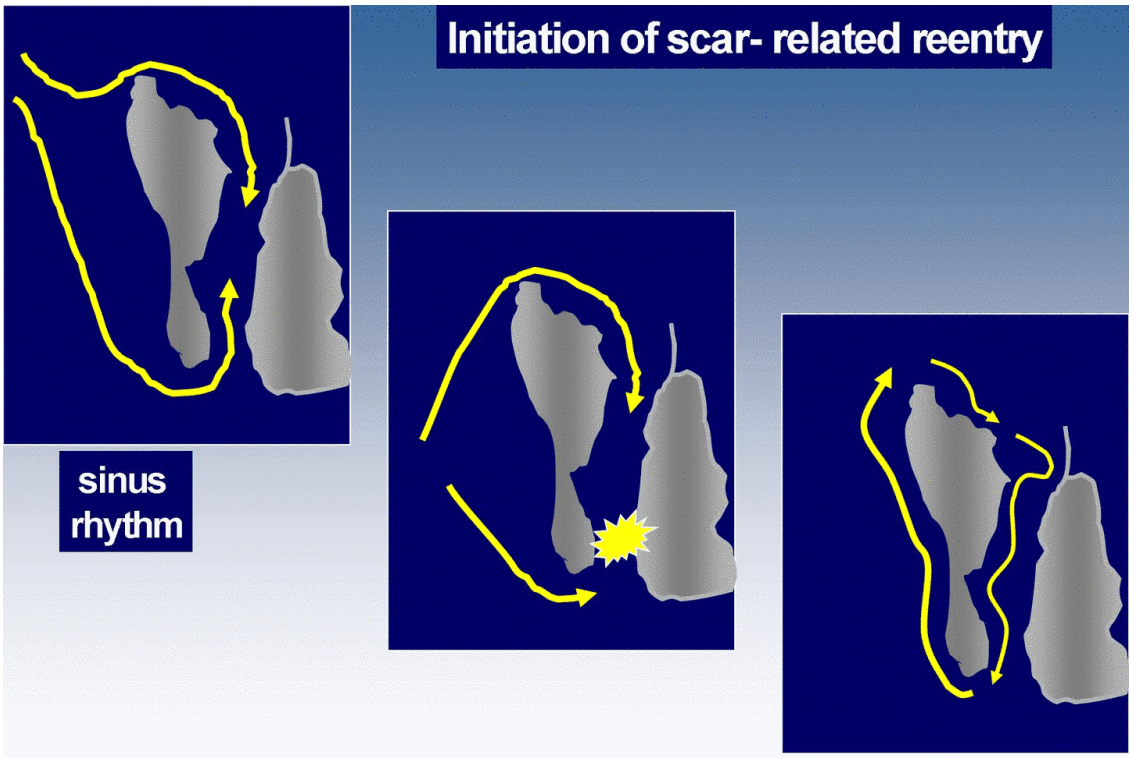
Spontaneous initiation of VT recorded from an ICD



First beat "initiation VT" has the same morphology as VT
30 – 50% of VT episodes

Roelke et al JACC; 23: 117 – 122
Saeed et al AJC 2000;85:580-7.

Initiation of scar- related reentry



Scar-related Reentry

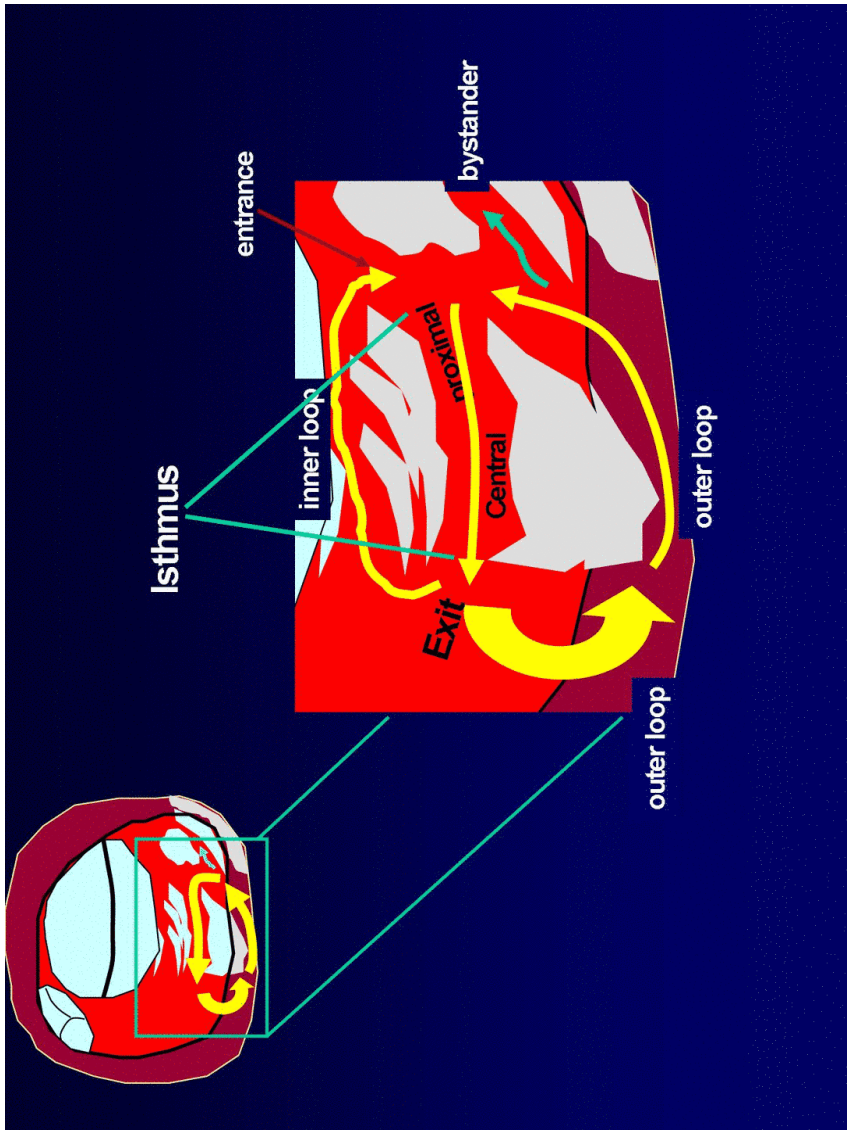
- Substrate is "relatively fixed"
- Stable reentry circuits that can cause repeated VT episodes over years
- VT is inducible with pacing
- Efficacy of antiarrhythmic drugs is poor

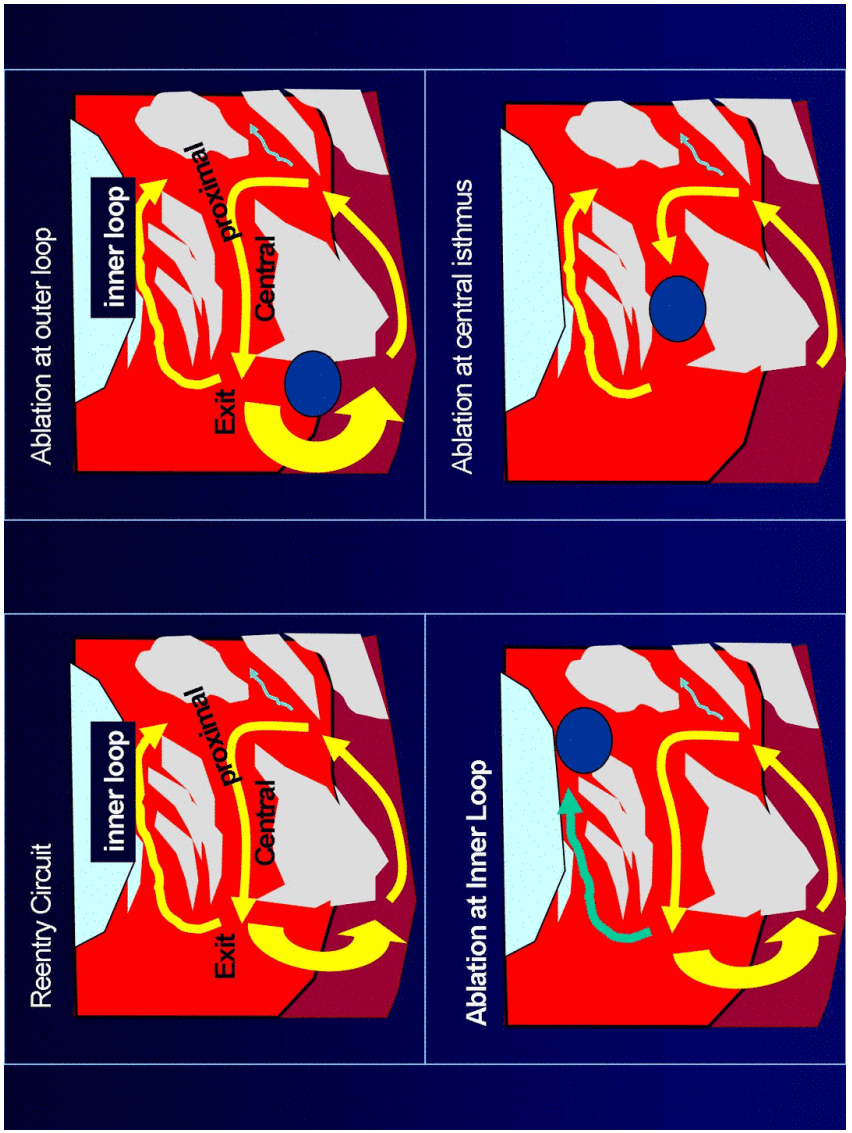
Sources of Ventricular Scar

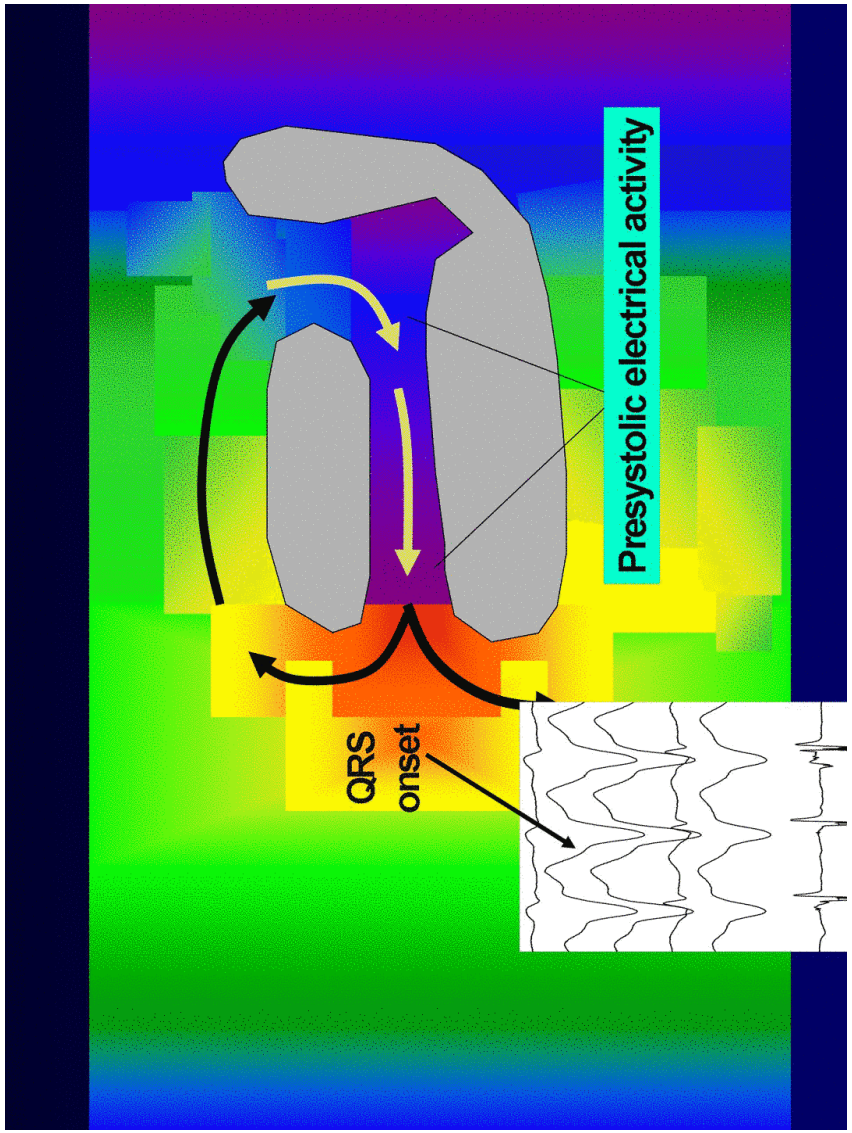
Myocardial infarct
Cardiomyopathy
ARVC
Sarcoidosis
Prior ventricular surgery

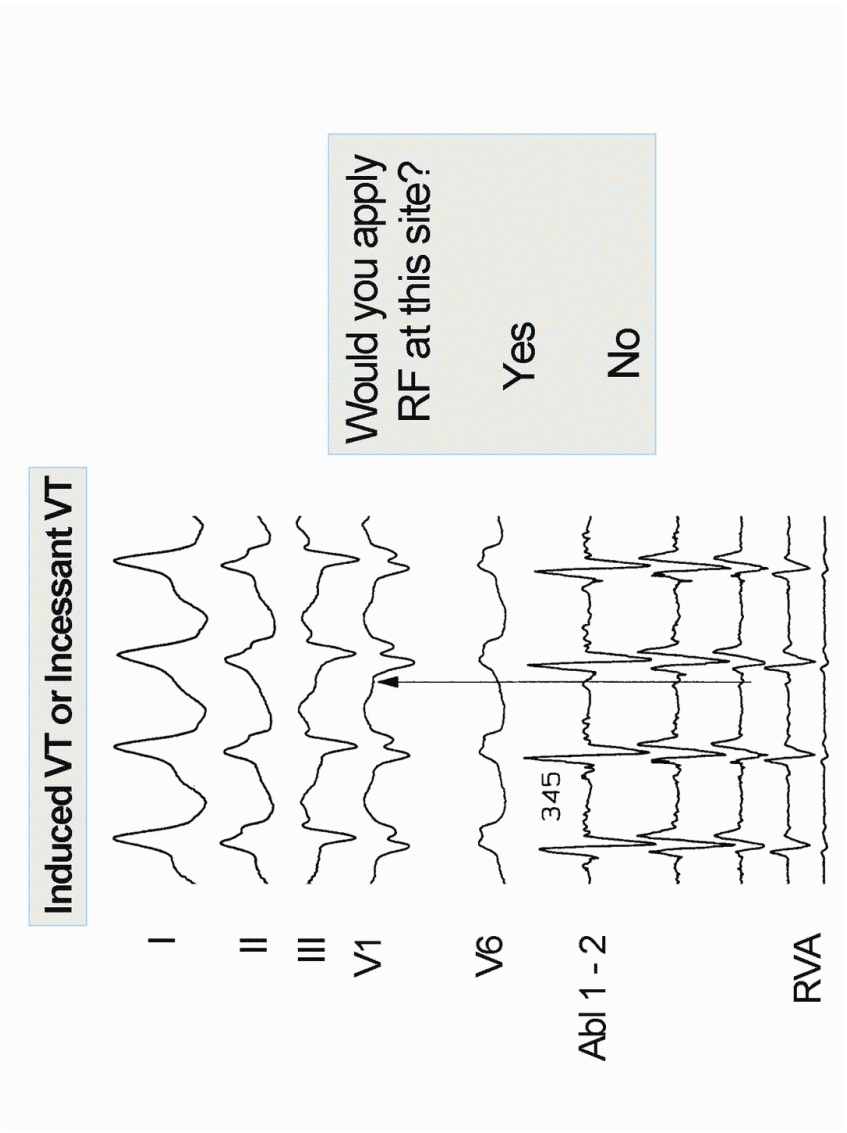
Scar-related Reentry Challenges for Ablation

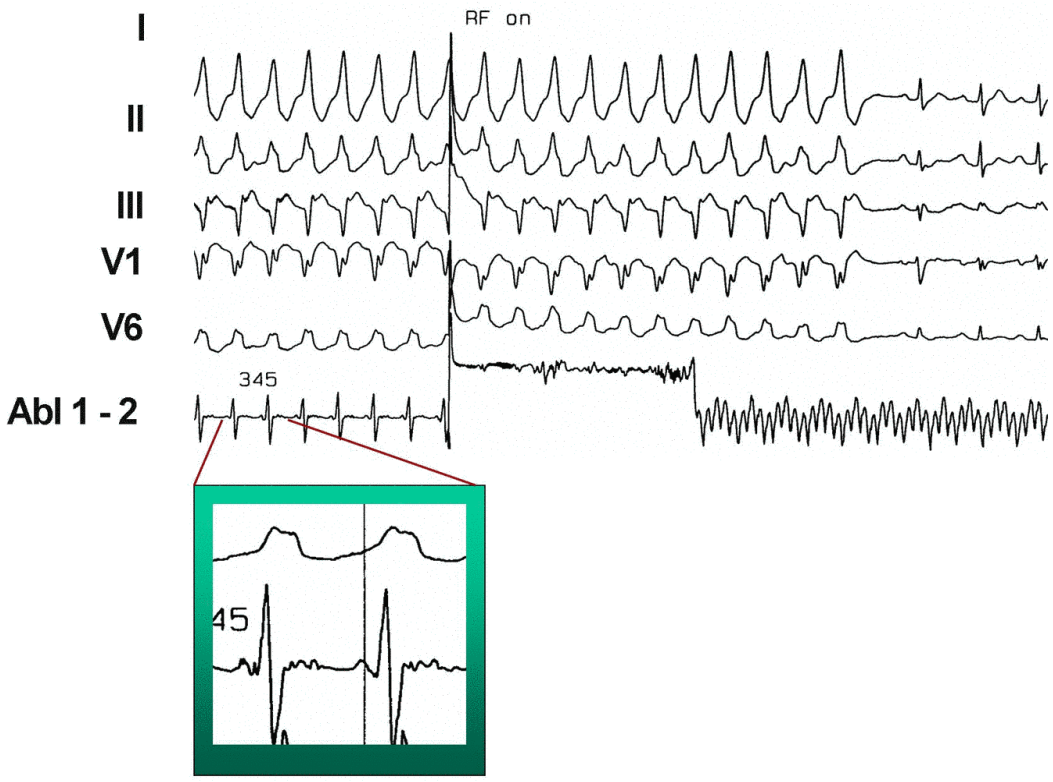
- Areas of scar are often large
- Reentry circuits can be large
- Multiple potential reentry circuits exist
- Complex electrograms with multiple components complicate mapping
- Bystander regions – cause abnormal electrograms at sites outside the circuit
- Unstable tachycardias that allow limited mapping during VT are common


Isthmus
entrance
inner loop
bystander
proximal
Central
Exit
outer loop
outer loop


Reentry Circuit
inner loop
proximal
Central
Exit
Ablation at outer loop
inner loop
proximal
Central
Exit
Ablation at Inner Loop
Ablation at central isthmus


Presystolic electrical activity
QRS onset


Induced VT or Incessant VT
Would you apply RF at this site?
Yes
No
I
II
III
V1
V6
Abl 1 - 2
345
RVA



Entrainment mapping defines the relation of a single pacing site to the reentry circuit based on the response to electrical stimulation at the site

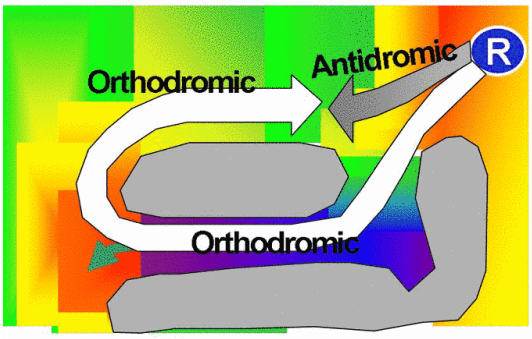
Entrainment mapping answers two questions:

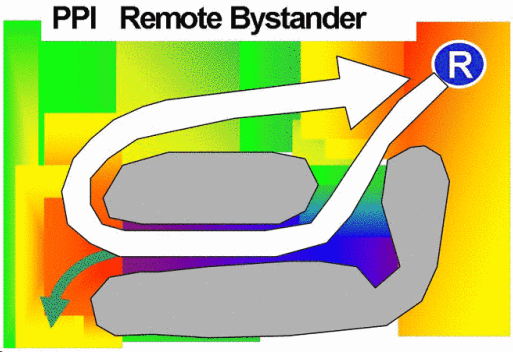
Is the pacing site in the reentry circuit?

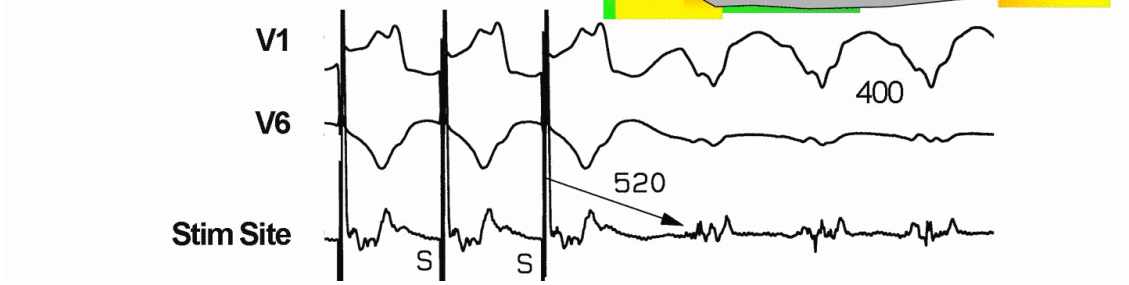
Is the site at a narrow isthmus in the reentry circuit?

The post pacing interval indicates if the site is in the circuit

PPI = conduction time from pacing site to circuit
+ revolution time through circuit
+ conduction time from circuit back to pacing site



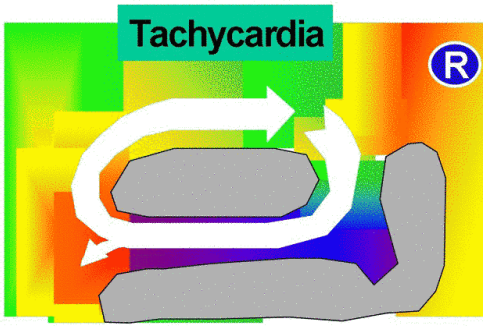


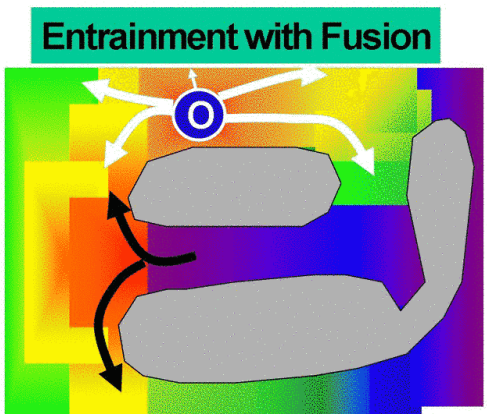


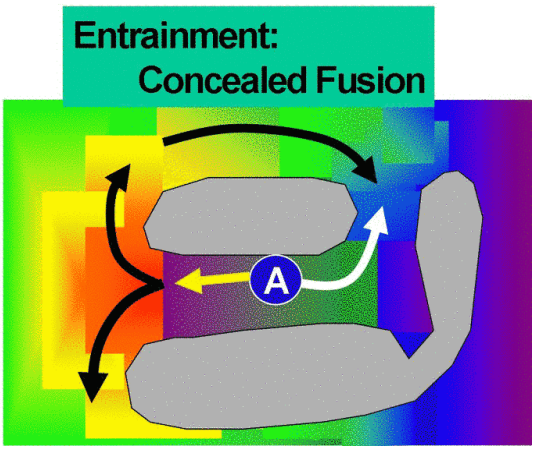
Broad Loop - fusion is overt
= QRS different from VT

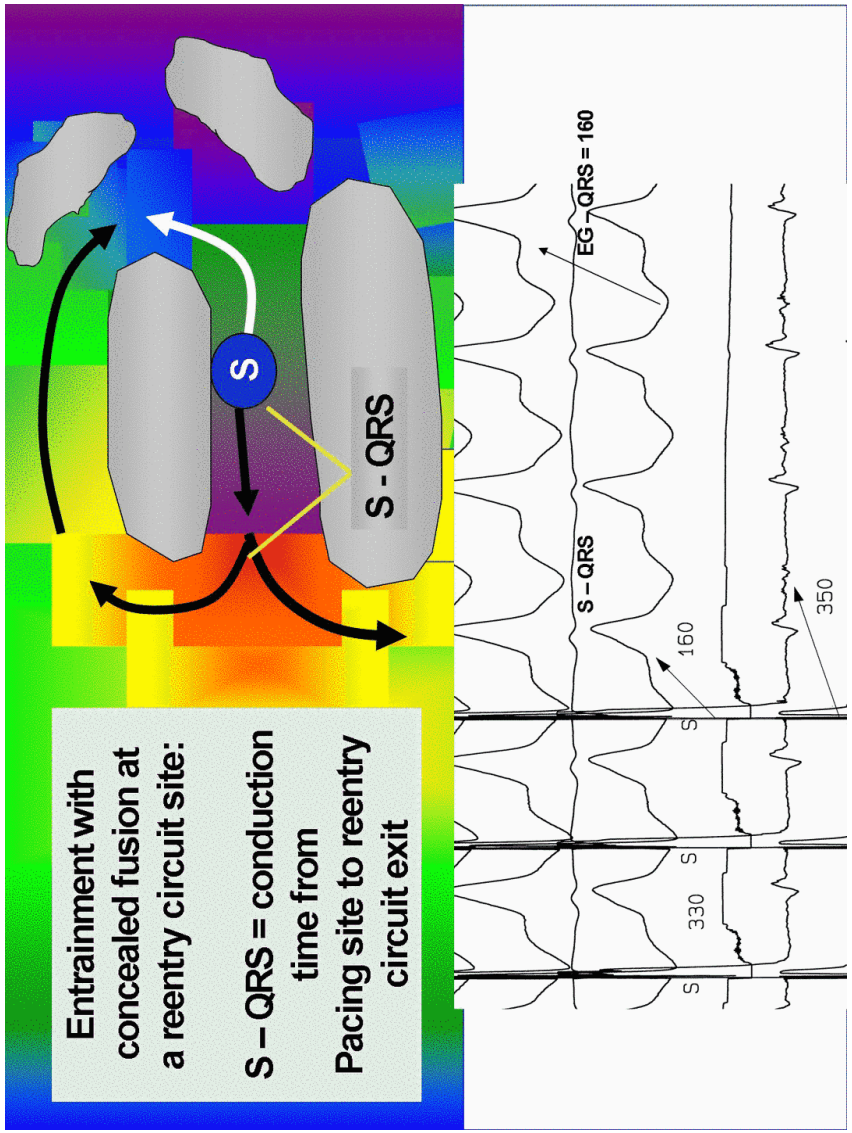
versus

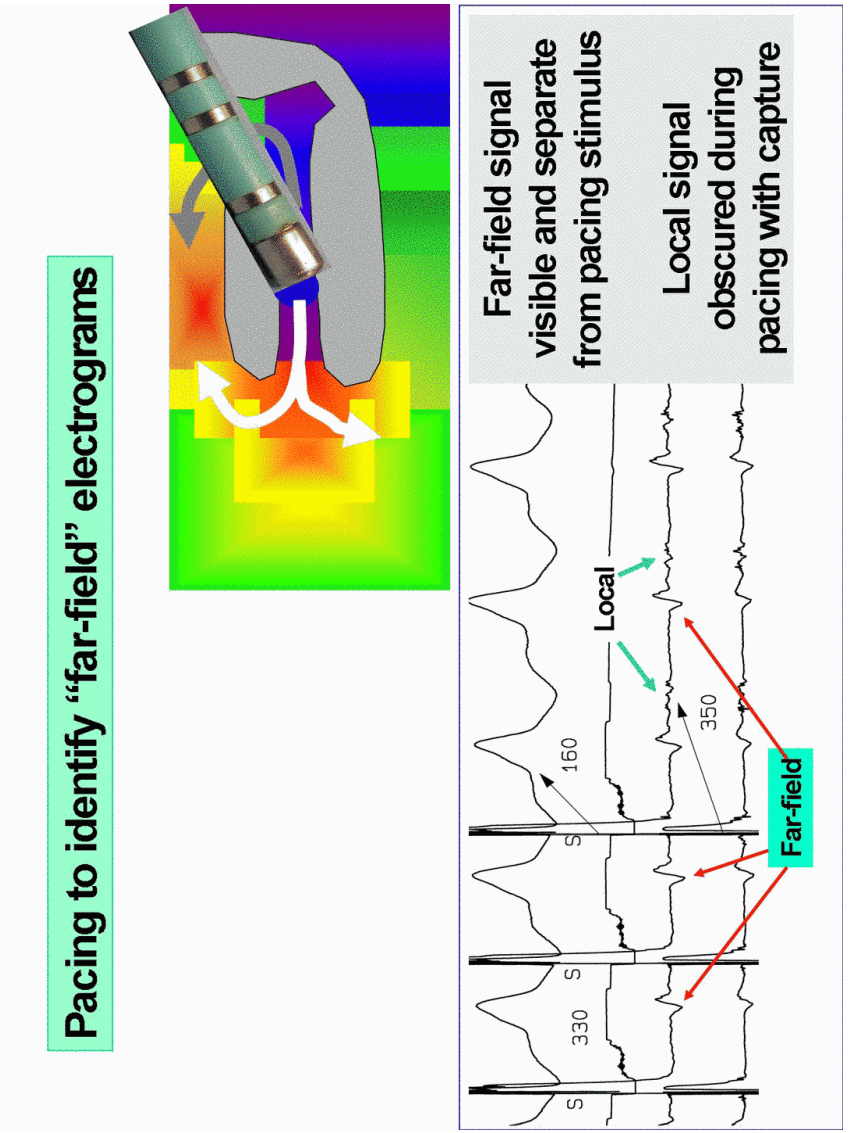
Isthmus (channel)
fusion is concealed
= QRS same as VT





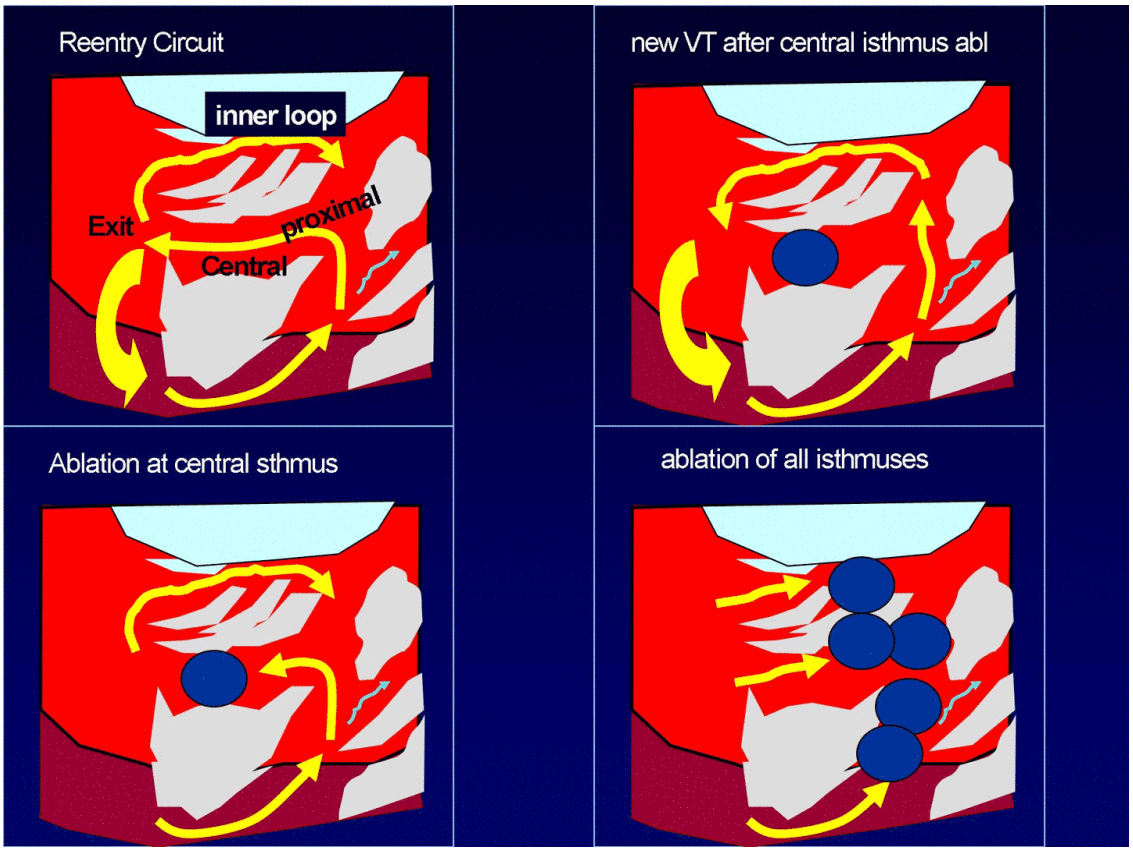



Entrainment with concealed fusion at a reentry circuit site:
S – QRS = conduction time from Pacing site to reentry circuit exit
S
S - QRS
EG – QRS = 160
S – QRS
160
330
350
S


Pacing to identify "far-field" electrograms
Far-field signal visible and separate from pacing stimulus
Local signal obscured during pacing with capture
Local
Far-field
160
330
350
S

Entrainment Mapping

- **Advantages**
  - Does not require recordings from multiple sites to determine the relation of the pacing site to the reentry circuit
  - Stimulus capture indicates electrode contact and tissue viability
- **Problems**
  - Requires "stable" tachycardia
  - Undesirable pacing effects
    - tachycardia termination or acceleration



Substrate Guided Approaches to Ablation of Multiple and Unstable Scar VTs during stable sinus rhythm

Identify the scar / infarction – low voltage bipolar EGs <1.55mV

Marchlinski Circ 2000;101:1288; Reddy *JACC* 2003;41:2228

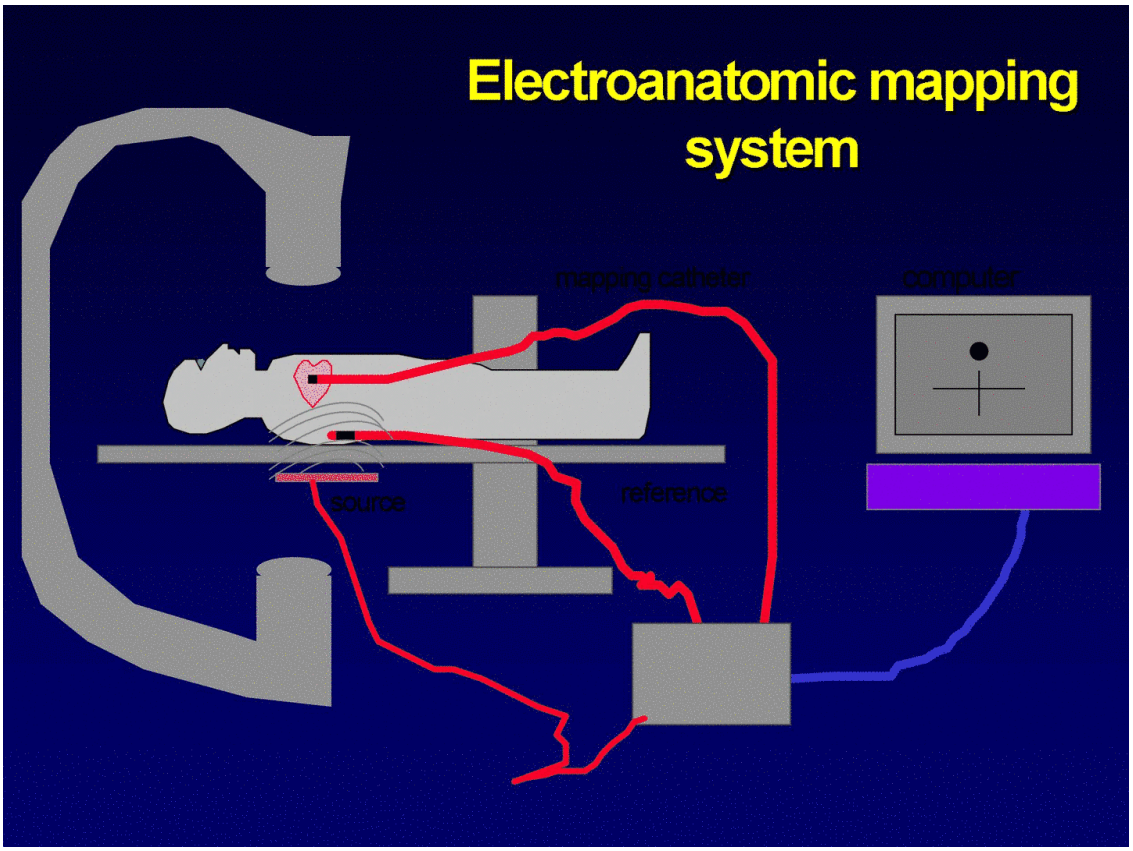
Identify exits in the scar border - pace mapping / QRS

Marchlinski 2000, Reddy 2003, Kottkamp 2003, Bruckhorst 2004

and / or

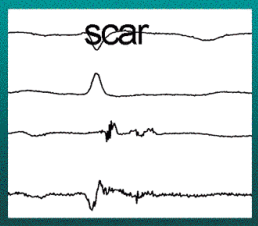
Identify Channels / Isthmuses

- Electrically unexcitable scar
  Soejima 2002
- Pace-mapping for slow conduction and QRS morphology
  Brunckhorst 2004, Reddy 2003, Kottkamp 2003
- Isolated potentials (SR or V pacing)
  Arenal 2004, Nakagawa 2004 abst
- EG amplitude - Arenal 2004

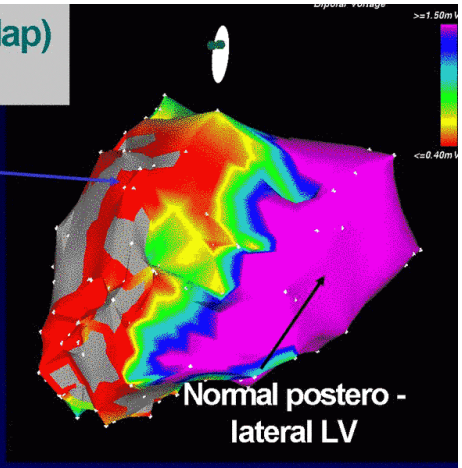


Electrogram Amplitude Map (Voltage Map) of the Left Ventricle

Abnormal Electrograms



Low Voltage Infarct Region

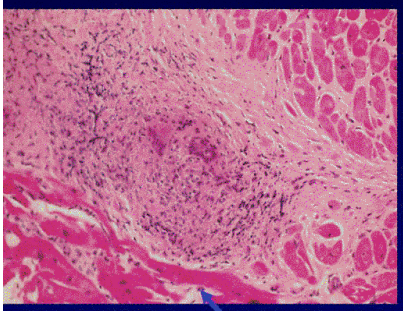


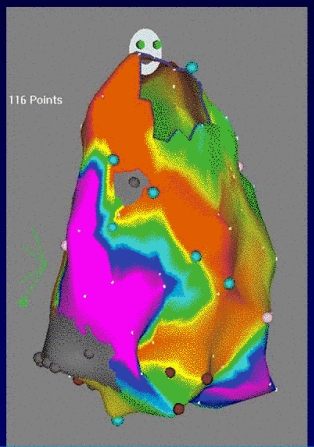
- 95% of normal LV electrograms > 1.55 mV **Marchlinski et al Circ 2000;101:1288; Reddy et al. *JACC* 2003;41:2228**
- Low amplitude region correlates well with histologic region of infarction in animal models **Callans, et al. Circulation, 1999. 100: 1744. Gepstein, et al. Circulation, 1998. 98: 2055. Komowski, et al. Circulation, 1998. 98:1116.**

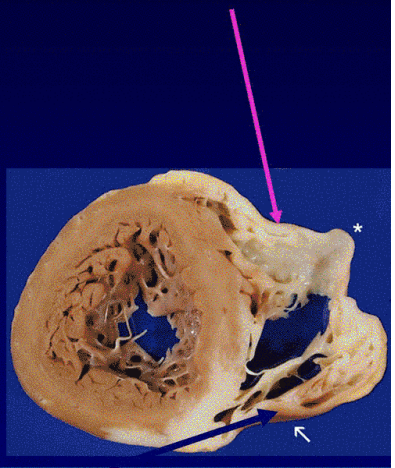
(bipolar 4 mm tip to 2 mm ring electrode, filtered at 10 – 30 to 400 Hz)

Two types of low voltage regions:

Electrically unexcitable scar (EUS)
- **dense fibrosis high pacing threshold**
- **potential reentry circuit border**

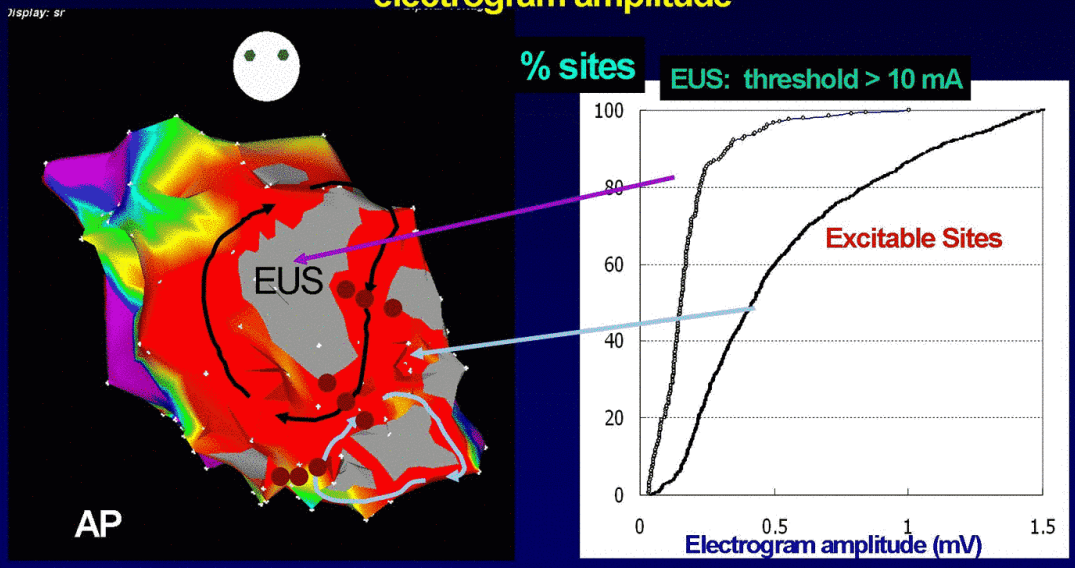






Reduced volume of myocytes – surrounding fibrosis
Conducting myocytes - potential reentry circuit channels

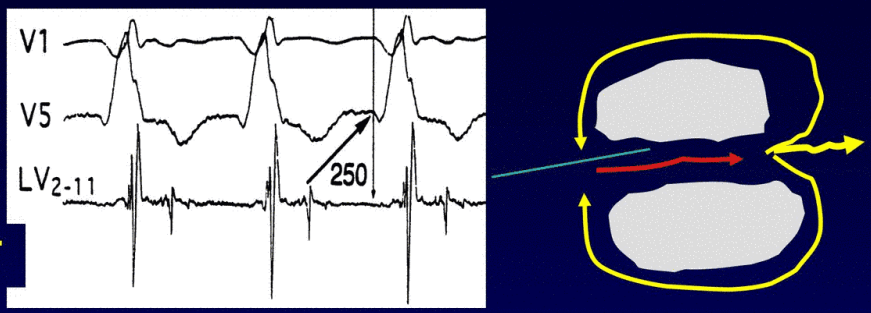
Electrically unexcitable scar (EUS) : Pacing threshold provides complimentary information to electrogram amplitude

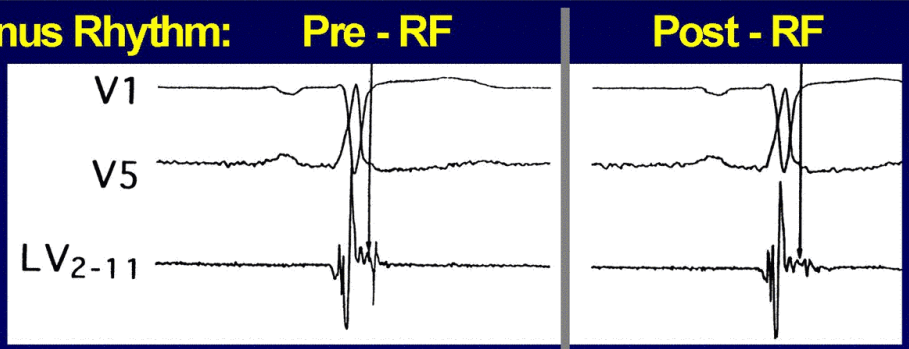


Soejima et al Circ 2002;106:1678

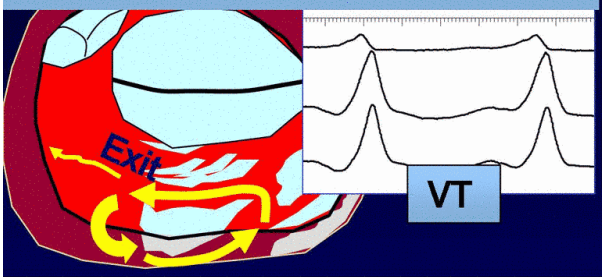
Relation of endocardial sinus rhythm late potentials to the reentry circuit

Harada et al JACC 1997; 30:1015



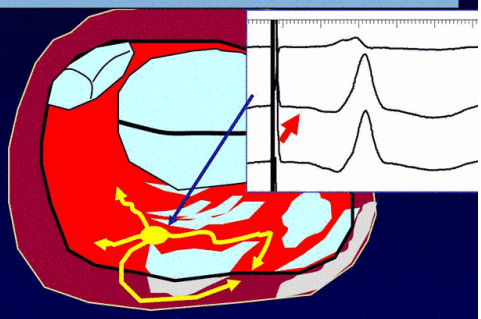


Pace-mapping during sinus rhythm for finding channels



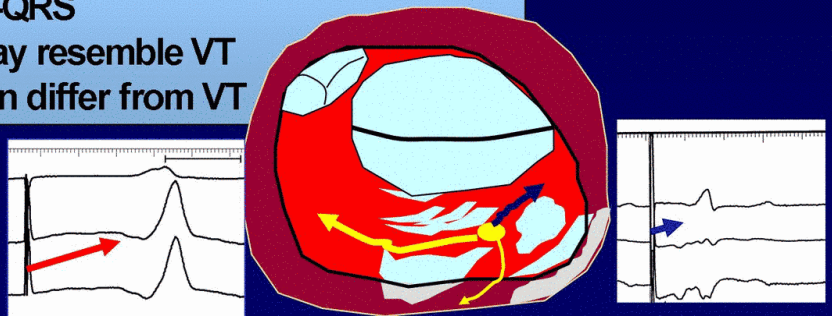
Pace-mapping at exit

QRS = VT morphology
Short S-QRS



Pace-mapping in the circuit proximal to the exit

- Long S-QRS
- QRS may resemble VT
- QRS can differ from VT

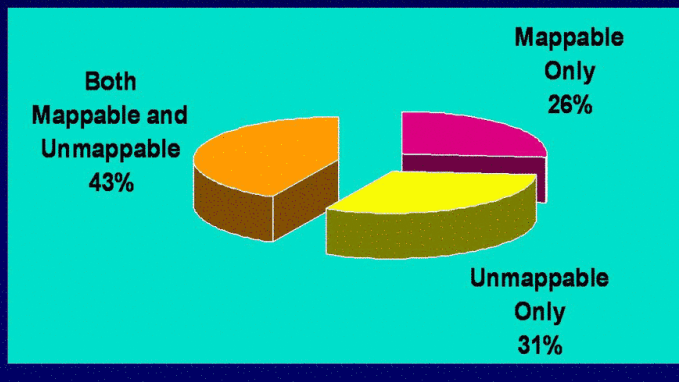


Bruncklhorst CB, et al. Circu*lation*. 2004;110:652-9.

Multicenter trial of VT Mapping and Ablation in 226 Patients with Prior Myocardial Infarction

Wilber, Stevenson et al HRS 2005

- Frequent VT failing therapy
  - Median of 11 episodes / 6 months or incessant
- Average LVEF 0.28
- Median 3 inducible VT morphologies / pt



Decrease in VT frequency after ablation

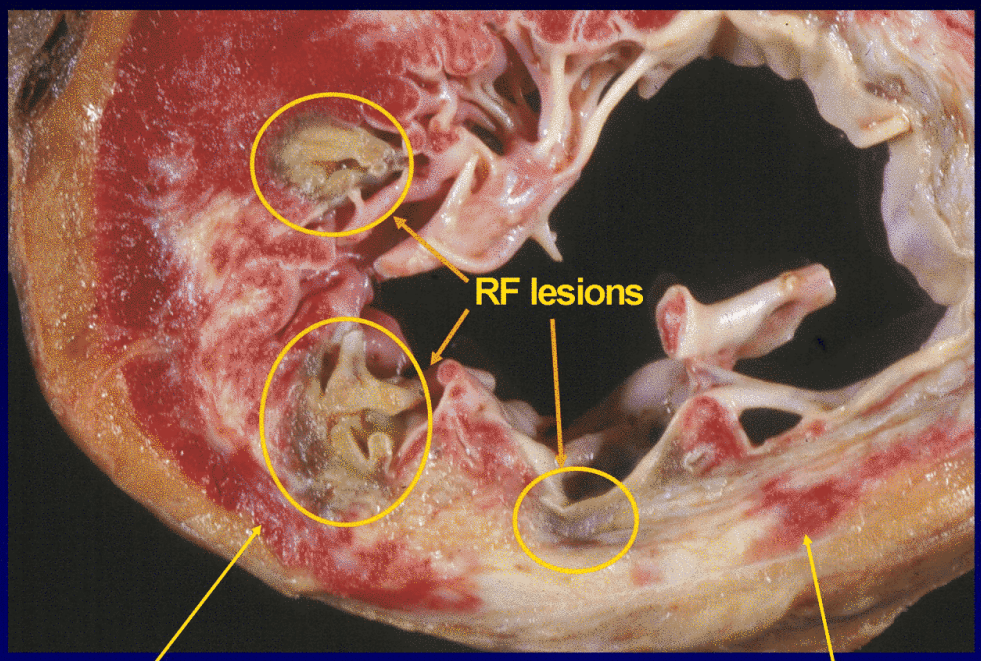
Wilber, Stevenson et al HRS 2005

Effect on Intermittent VT:

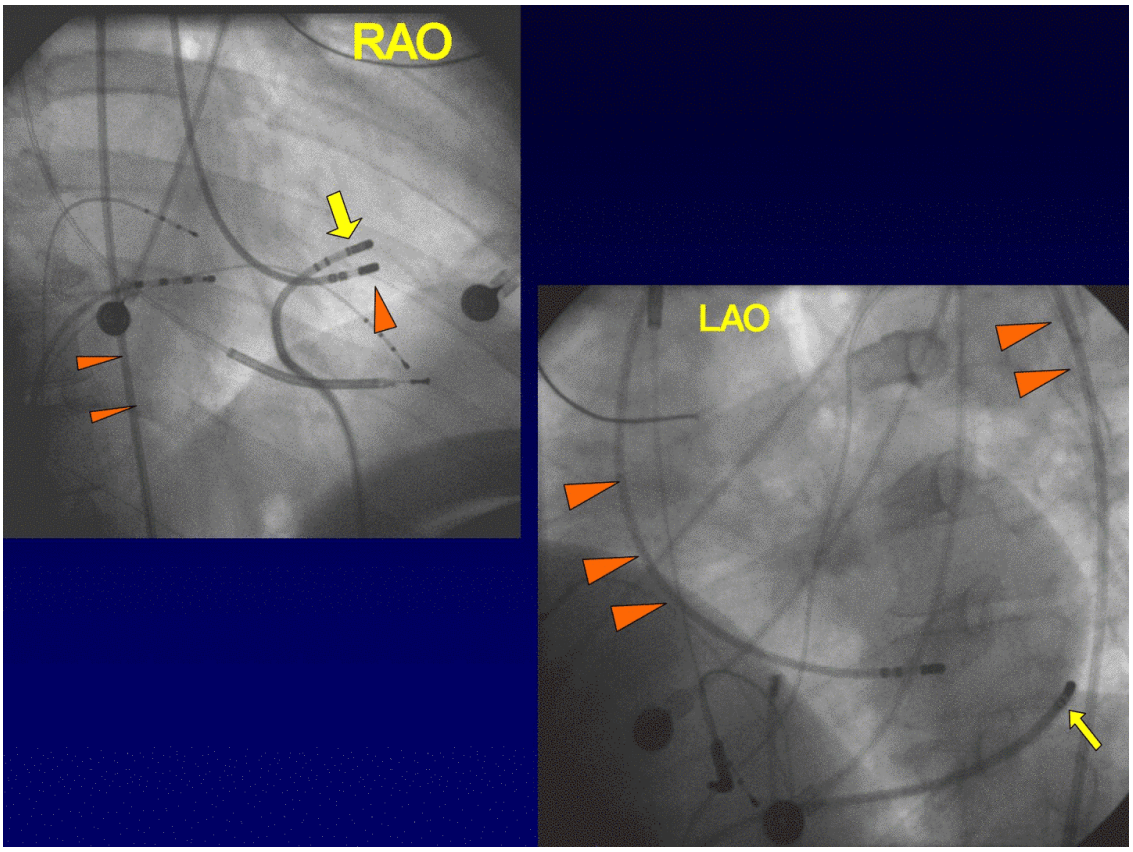
	% Patients with > 75% reduction in VT
Mappable VT	85%
Both	77%
Unmappable VT	67%

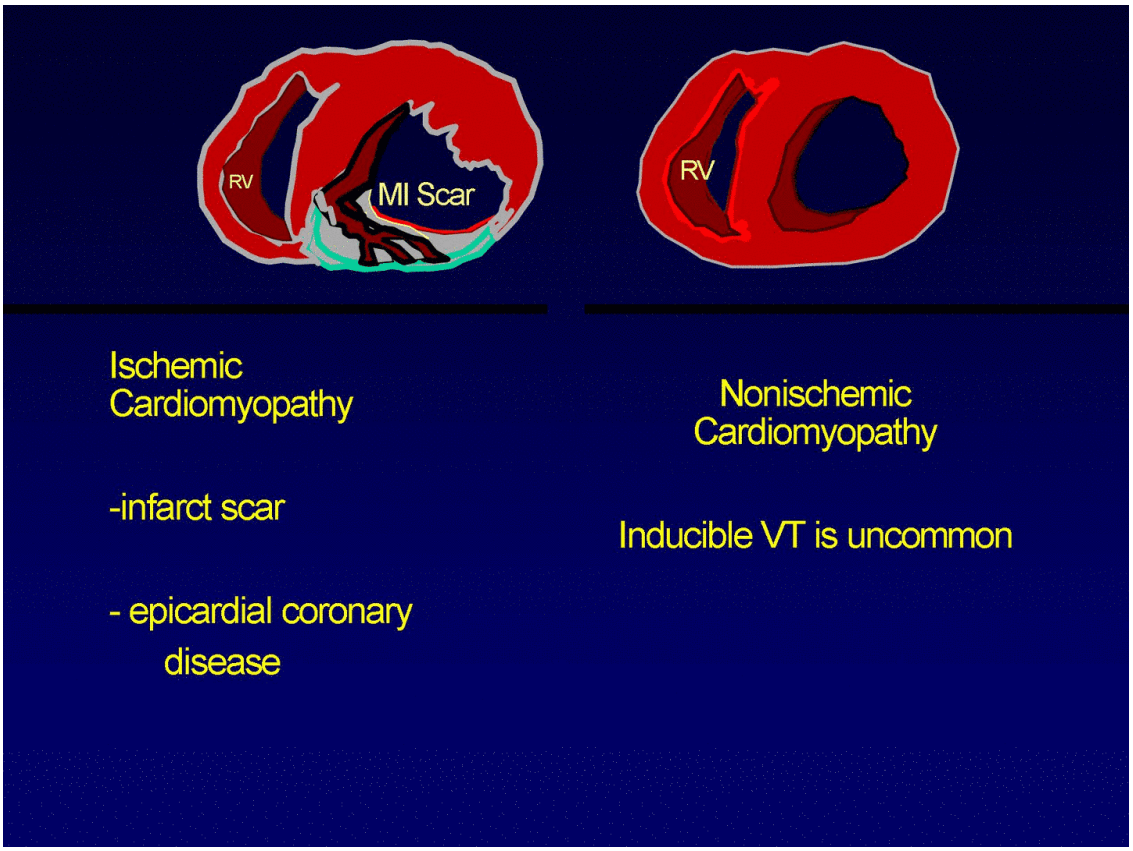
No diffence in outcome according to type of VT

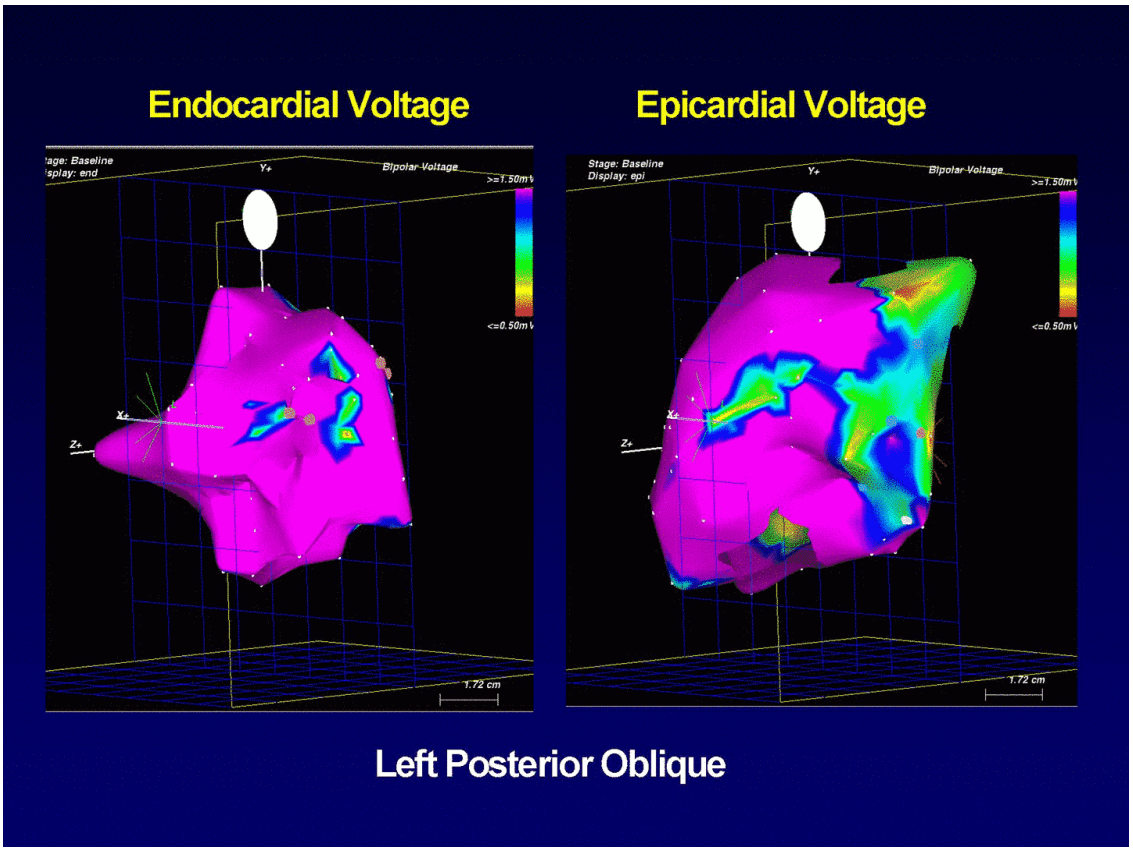
Incessant VT :
controlled in 83% of patients



Potential Reentry Circuits Deep to the Endocardium

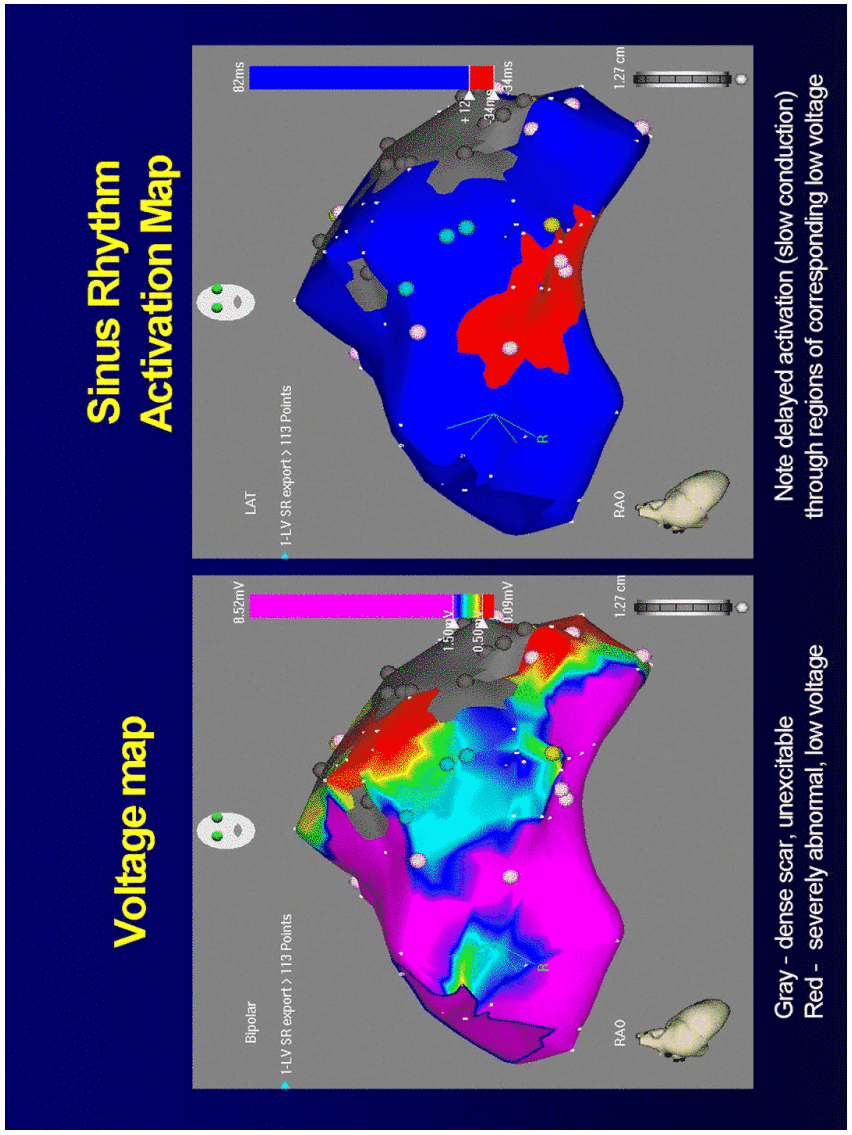

RAO
LAO

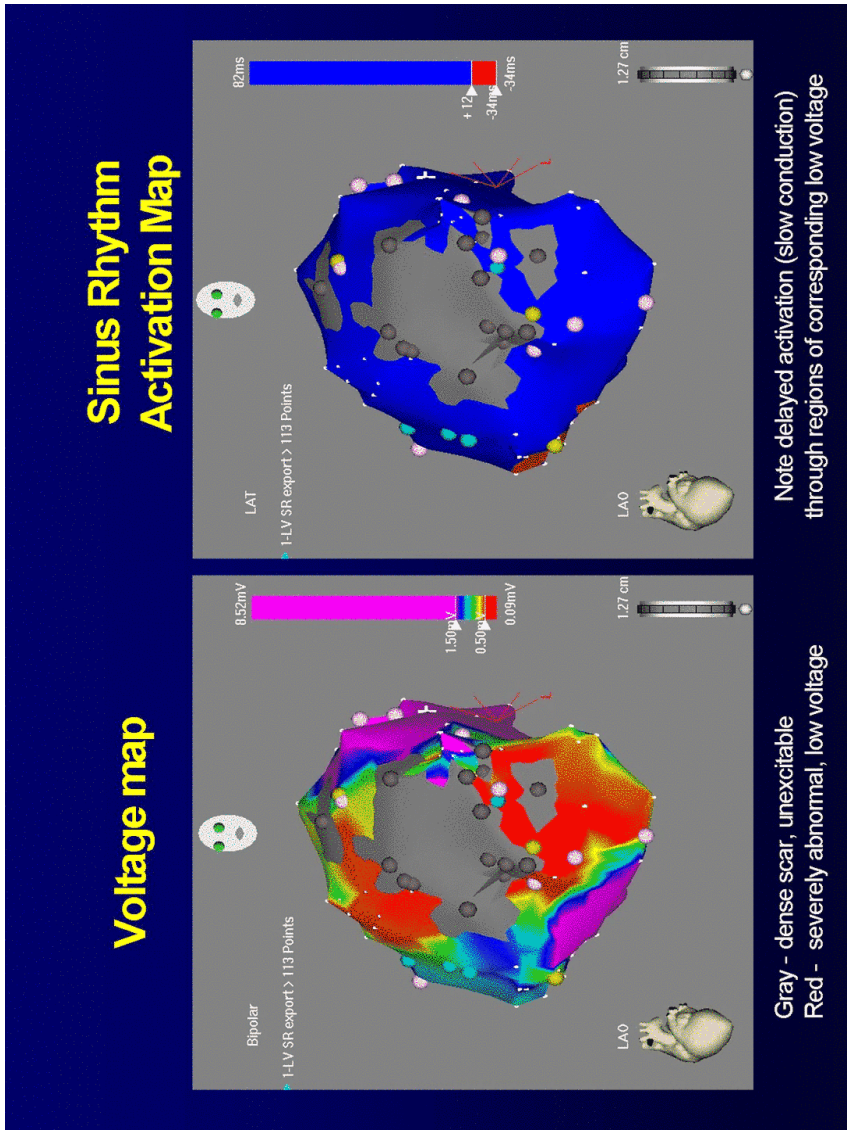

RV
MI Scar
RV
Ischemic
Cardiomyopathy
-infarct scar
- epicardial coronary
disease
Nonischemic
Cardiomyopathy
Inducible VT is uncommon



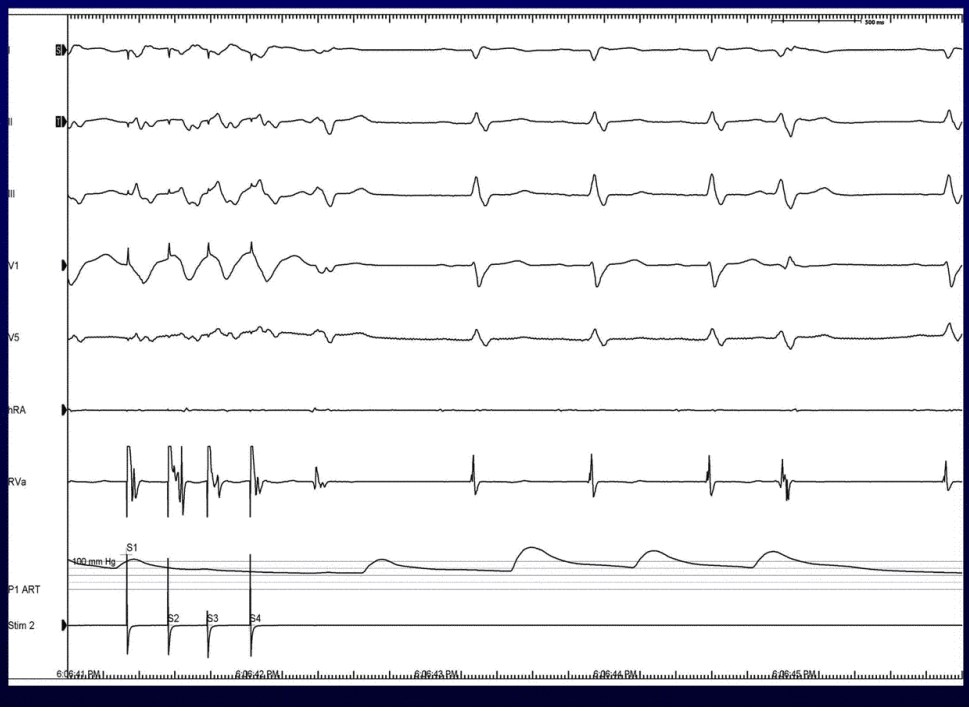
Case 1

Symptomatic VT
Anterior wall MI 20 years ago


Sinus Rhythm
Activation Map
LAT
1-LV SR export > 113 Points
82ms
+ 12
-34ms
1.27 cm
RAO
Note delayed activation (slow conduction)
through regions of corresponding low voltage
Voltage map
Bipolar
1-LV SR export > 113 Points
8.52mV
1.50mV
0.50mV
0.09mV
1.27 cm
RAO
Gray - dense scar, unexcitable
Red - severely abnormal, low voltage


Sinus Rhythm
Activation Map
LAT
1-LV SR export > 113 Points
82ms
+ 12
-34ms
1.27 cm
LAO
Note delayed activation (slow conduction)
through regions of corresponding low voltage
Voltage map
Bipolar
1-LV SR export > 113 Points
8.52mV
1.50mV
0.50mV
0.09mV
1.27 cm
LAO
Gray - dense scar, unexcitable
Red - severely abnormal, low voltage

No Inducible VT at Conclusion



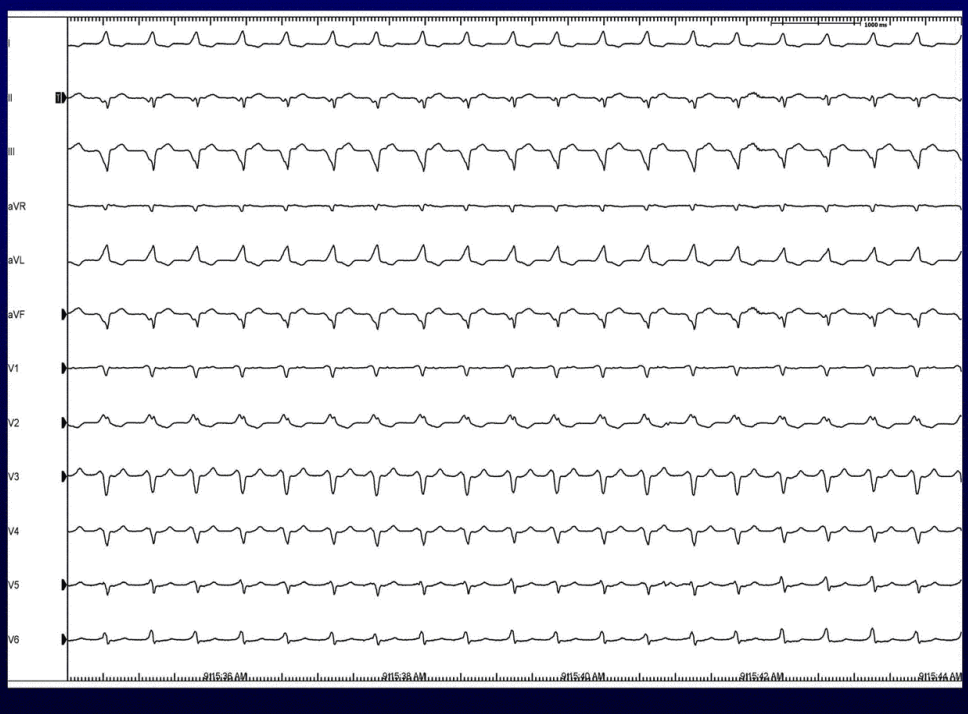
Case 2

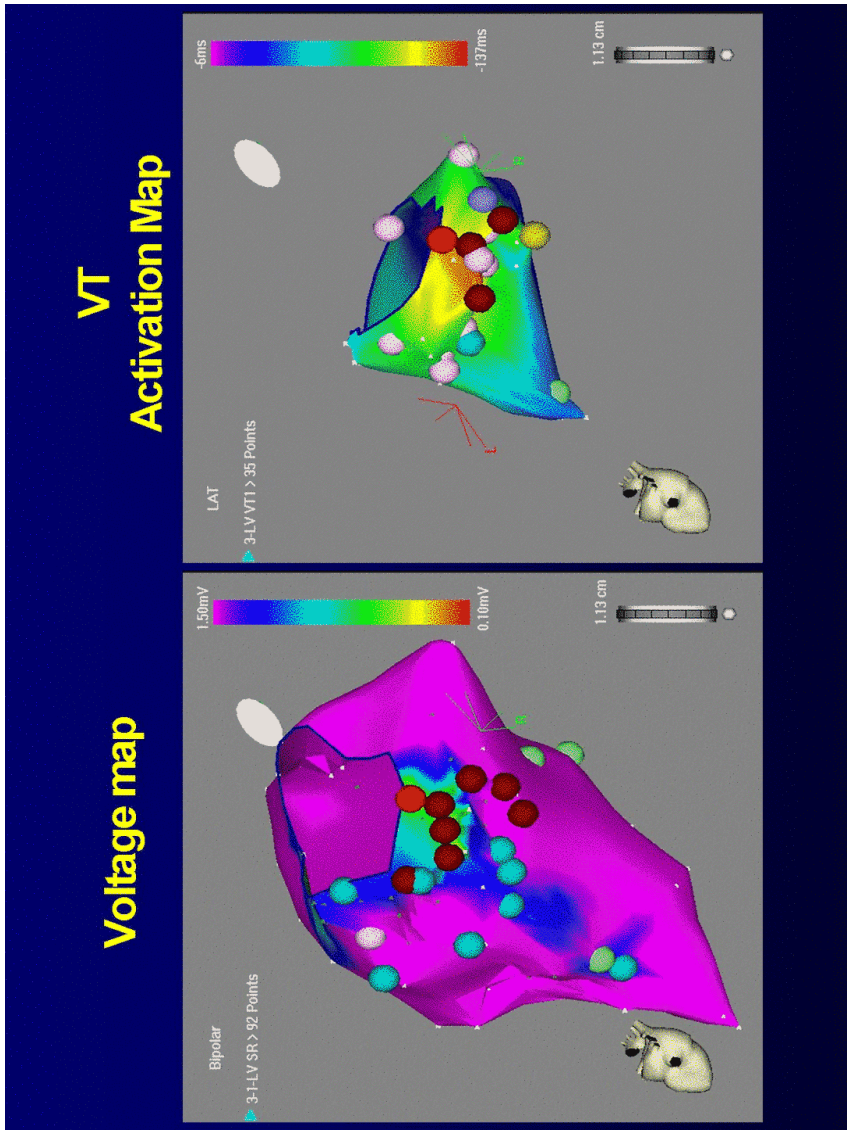
- 44yo M – diabetic, hypertensive
- January 2005
  - Inferior MI
- February 2005
  - Presents with wide QRS tachycardia
  - ICD implanted
  - Recurrent VT → sotalol
- January 2006
  - Incessant VT → amiodarone ineffective
  - Rx: atenolol 25mg, lisinopril 40mg, simvastatin 40mg, amlodipine 5mg, ECASA 325mg, metformin, glipizide
  - Transferred to BWH

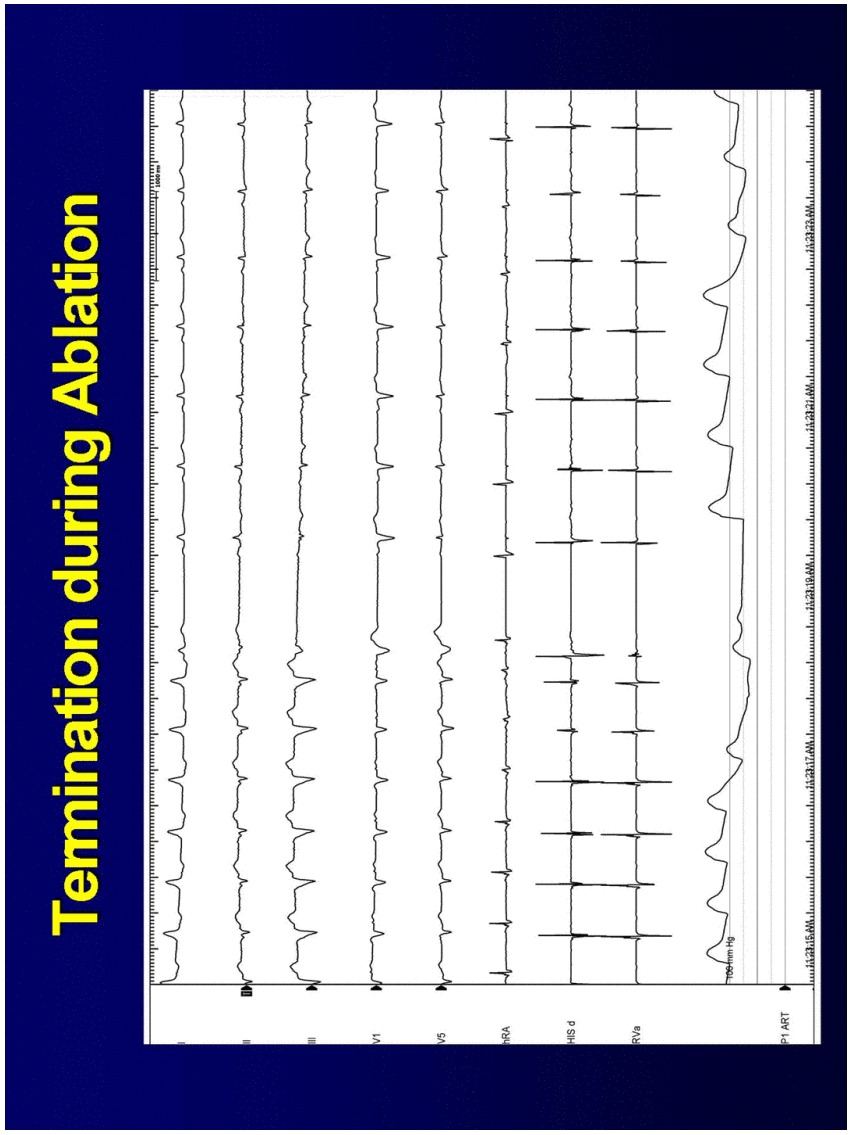
Case 2

Incessant VT
Inferior wall MI 1 year ago

Presenting Rhythm at Baseline



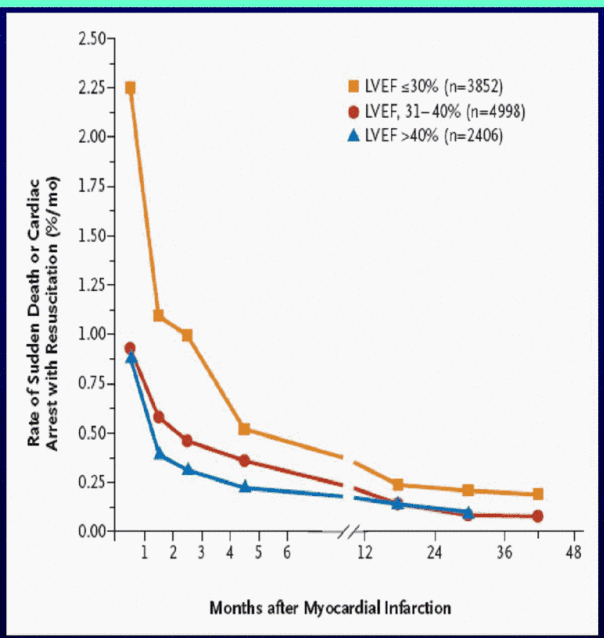

Voltage map
Bipolar
3-1-LV SR > 92 Points
1.50mV
0.10mV
1.13 cm
VT
Activation Map
LAT
3-LV VT1 > 35 Points
-6ms
-137ms
1.13 cm


Termination during Ablation

A Tale of Two Infarcts

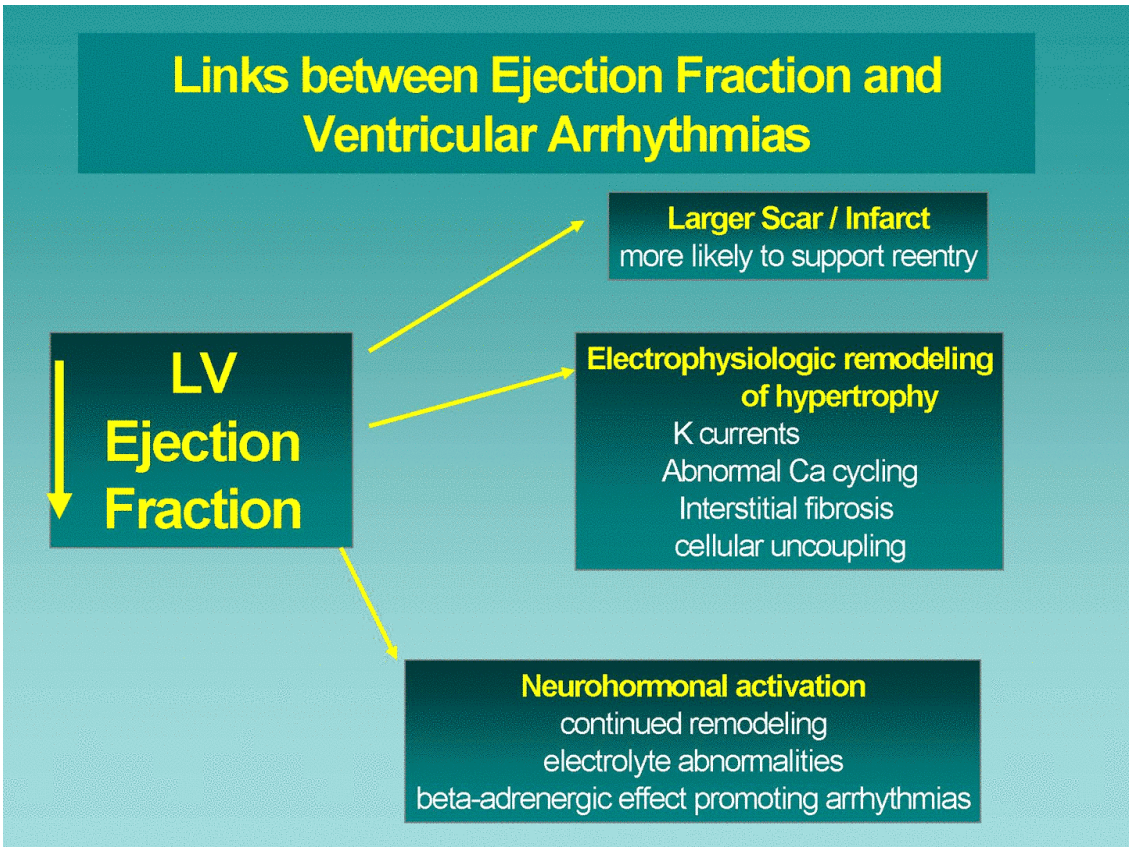
- Case 1
  - History of anterior MI
  - On ACE, statin, β-blocker
  - EF 20%
  - No revasc needed
  - No heart failure symptoms
  - VT *20 years* post MI
- Case 2
  - Inferior MI
  - On ACE, statin, β-blocker
  - EF 20%
  - No revasc needed
  - No heart failure symptoms
  - VT *6 weeks* post MI

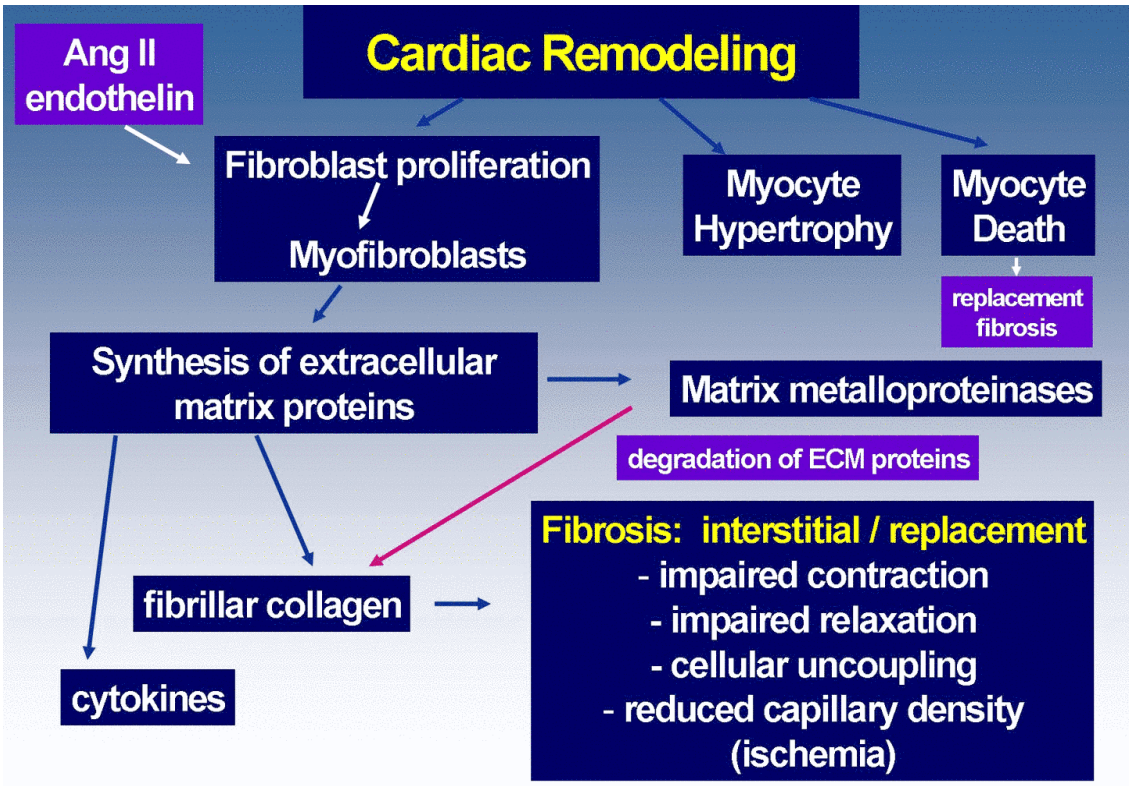
Risk of Sudden Death after Acute MI – VALIANT



Post-MI patients with reduced EF and/or CHF 0.5-10 days post-MI
Randomized to ARB or ACE or combination

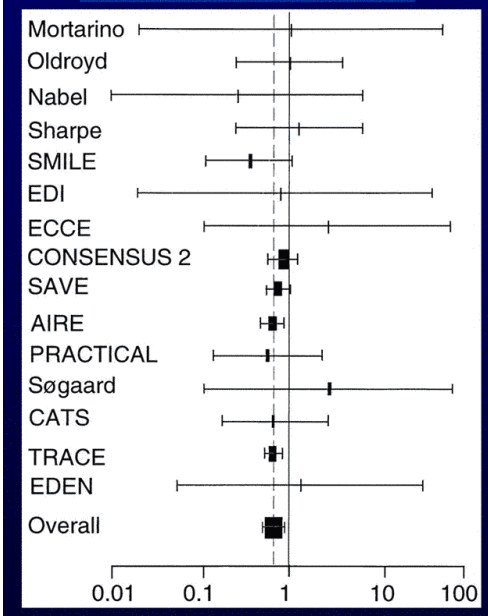
Solomon SD. *N Engl J Med*, 2005; 352: 2581-8





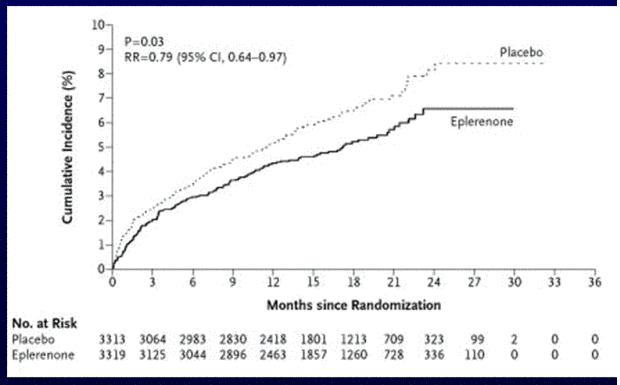
Manabe et al. Gene Expression in Fibroblasts and Fibrosis. Circ Res 2002;91:1103
Brown. Cardiac extracellular matrix: a dynamic entity. *AJP Heart Circ Physiol* 289: H973–H974, 2005;

ACE – inhibitors reduce sudden death after MI



Domanski, M. J. et al. J Am Coll Cardiol 1999;33:598-604

Eplerenone reduces sudden death after complicated acute MI

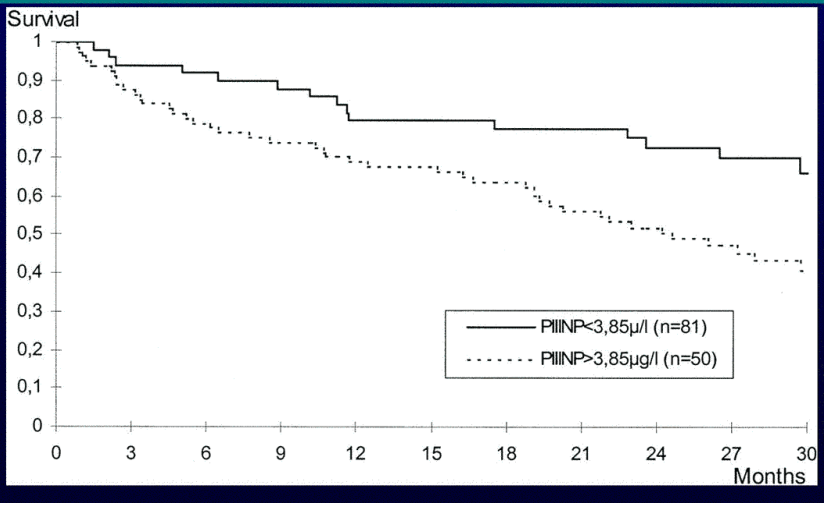


Pitt et al NEJM 2003; 348: 1409

RALES substudy: Zannad et al Circulation 2000;102:2700
spironolactone vs placebo for class III – IV CHF

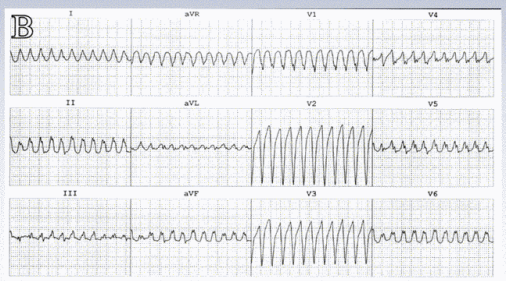
procollagen type III amino-terminal peptide (PIIINP) – marker of collagen synthesis

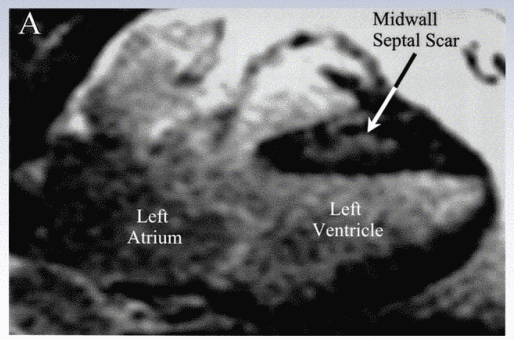
- level related to survival
- spironolactone reduced PIIINP during follow-up
- benefit confined to the population with > median PIIINP



MRI Assessment of the Substrate for Inducible VT in Nonischemic Cardiomyopathy

26 patients with nonischemic cardiomyopathy
- referred for EP evaluation or ICD
- 5 / 26 had inducible monomorphic VT
- VT was associated with larger, thicker LV regions of scar detected by MRI delayed hyperenhancement

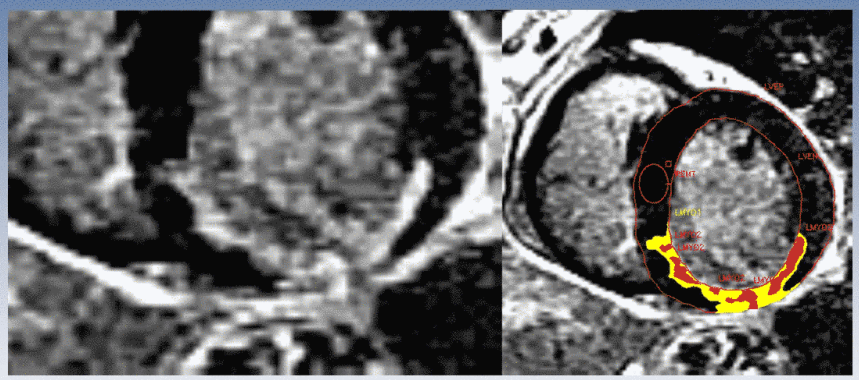




Nazarian, S. et al. Circulation 2005;112:2821-2825

Extent of Peri-Infarct Regions on Contrast -enhanced MRI Predicts Post-infarction Mortality

R Kwong et al AHA 2005



Automatated analysis
- infarct: signal intensity > 2 SD above remote reference
- peri-infarct 2 – 3 SD > reference (yellow)

1.5 T scanner with a 4- or 8-element phased array coil over the chest.
Images acquired during breath-holds with ECG gating

Will high risk patients be identified from ventricular tissue characteristics ?

Scar repair with cell therapies

Skeletal myoblasts

Resident cardiac stem cells

Mesynchymal stem cells

Bone marrow cells

Embryonic stem cells

Fibroblasts Can Be Genetically Modified to Produce Excitable Cells Capable of Electrical Coupling

Kizana et al Circulation 2005; 111: 394 - 398

- Forced myogenesis in human fibroblasts using lenti-virus ventor-mediated gene transfer
  - myogenic differentiation with expression of myosin
  - expression of calcium channels that allowed stimulation of calcium transients
- After concurrent expression of connexin43 dye transfer studies indicated coupling of connexin43 channels between some cells.
- In 8 of 54 cell pairs, an identical stimulus threshold for induction of Ca2+ transients suggest electrical coupling
- Fibroblasts can be genetically modified to produce excitable cells capable of electrical coupling.
- Gene-based repair of cardiac conduction defects may be feasible

Does skeletal myoblast injection into scar cause ventricular arrhythmias?

- Ventricular arrhythmias have occurred in over 20% of the initial 41 patients reported
- Skeletal myoblasts do not appear to electrically couple with myocytes
- Potential arrhythmia mechanisms
  - electrotonic effects of automaticity
  - local injury
  - immunologic reaction from trace protein

Wollert, K. C. et al. Circ Res 2005;96:151-163

Arrhythmias After Cell Transplantation for Myocardial Regeneration: Natural History or Result of the Intervention?

NS PETERS J Cardiovascular EP Nov 2005

Conductive Bridges in Cardiac Tissue
A Beneficial Role or an Arrhythmogenic Substrate?

Y Rudy. Ci*rculation Research* 2004;94:709.