

# Ventricular arrhythmias: Bringing the pieces together

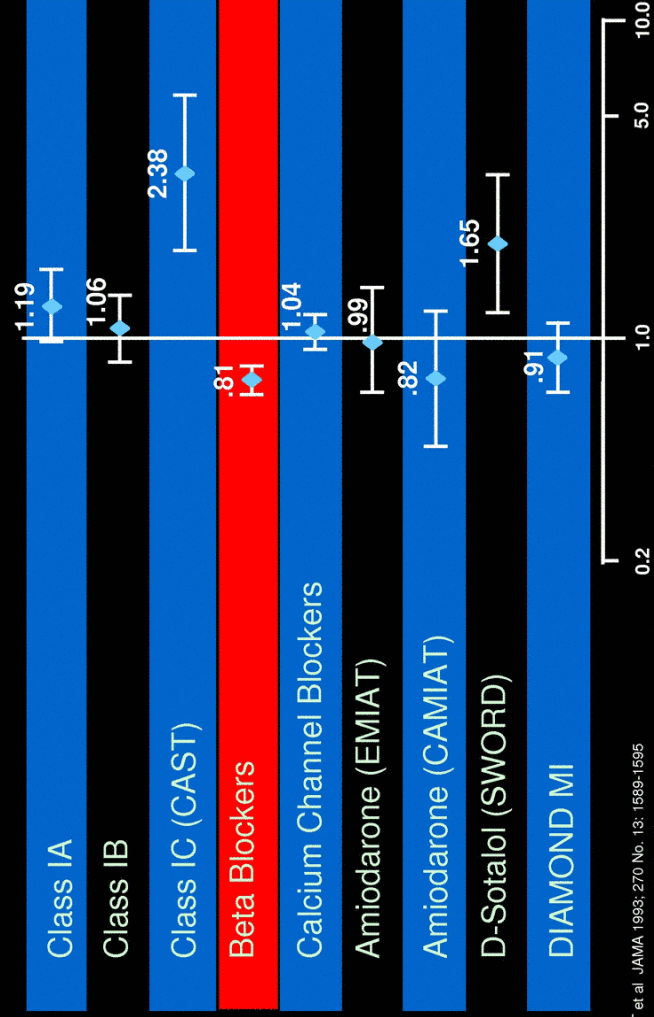
David S. Rosenbaum, M.D.



MetroHealth Campus,  
Case Western Reserve University



## Post-MI SCD Prophylaxis Trials



Teo KT et al. JAMA. 1993; 270 No. 13: 1589-1595  
 Echt D et al. NEJM. 1991; 324: 781-788  
 Julian DG et al. Lancet. 1997; 349: 667-674

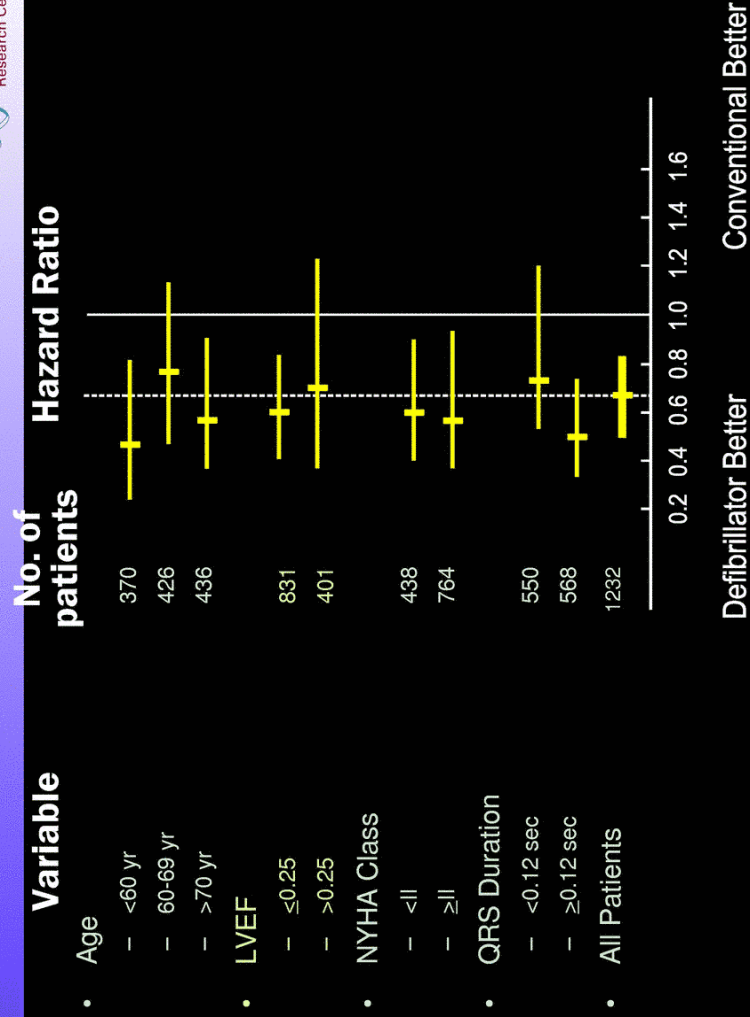
Waldo AJ et al. Lancet. 1996; 348: 7-12  
 Cairns, JA et al. Lancet. 1997; 349: 675-682

## Madit 2 Summary



- 5.5% absolute reduction in mortality at 2 yrs.
- Unexplained HF in ICD group
- In summary, 1 life saved for every 17 ICDs
- In Madit 1, 1 life saved for every 4 ICDs

## MADIT 2



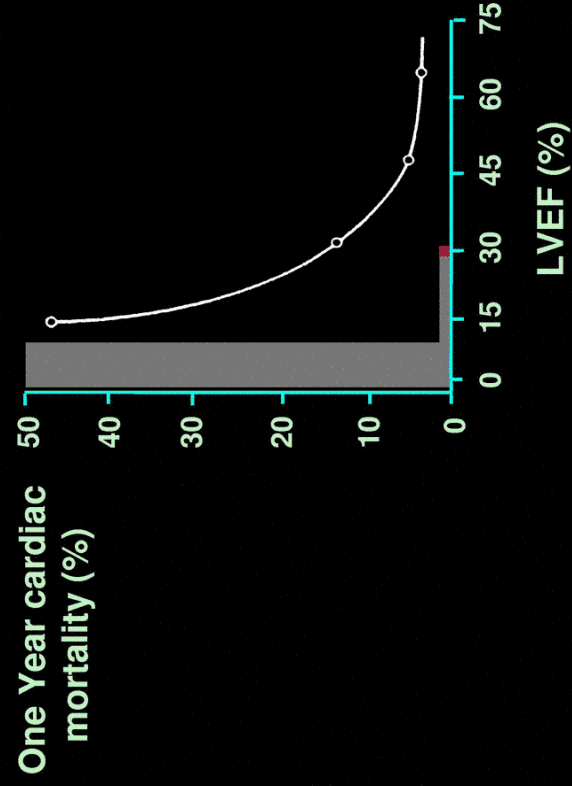
# Identifying the High Risk Patient



# LV dysfunction predicts cardiac events



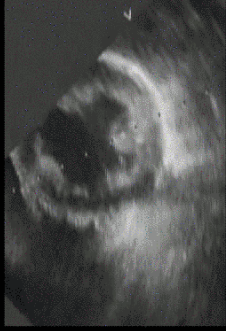
Multicenter Post-infarction Research Group. NEJM 1983;309:331



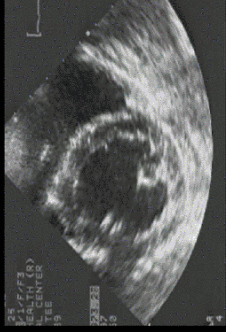
# Canine model of pacing-induced HF



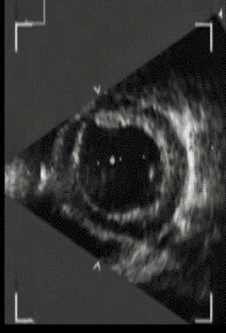
baseline



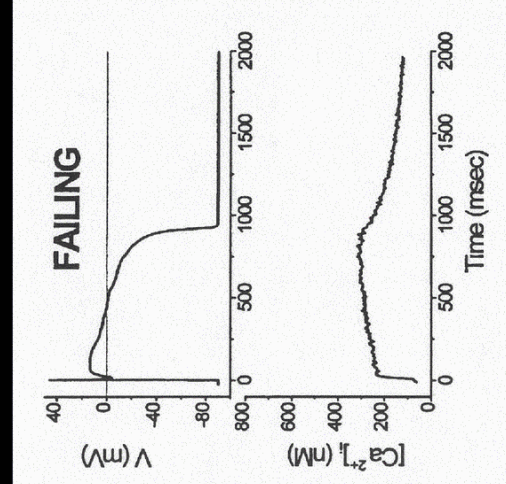
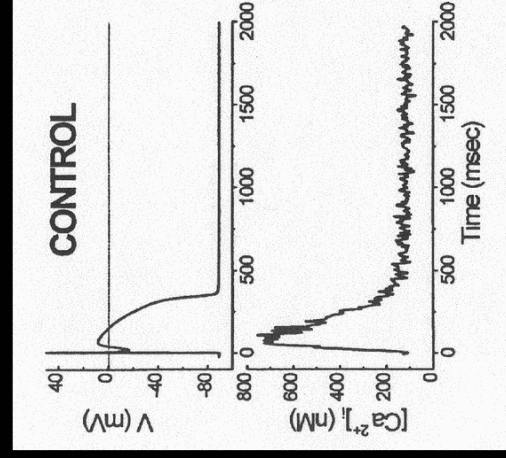
early



late

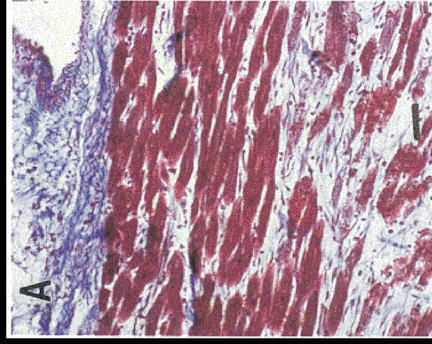


# Electrophysiological changes in heart failure

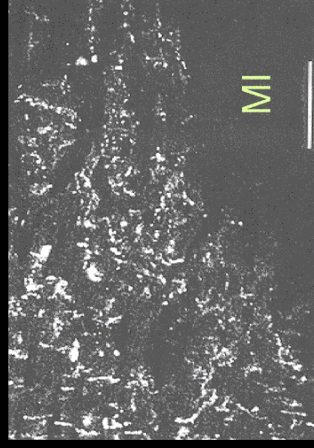


# Healed Myocardial Infarction

DOG



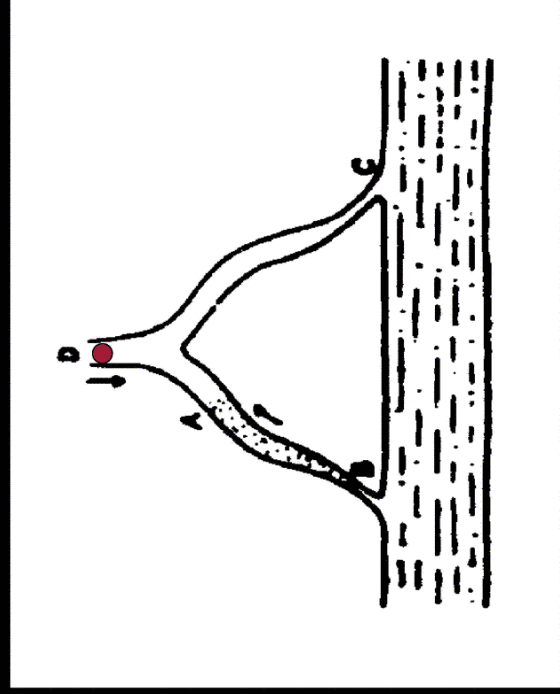
HUMAN



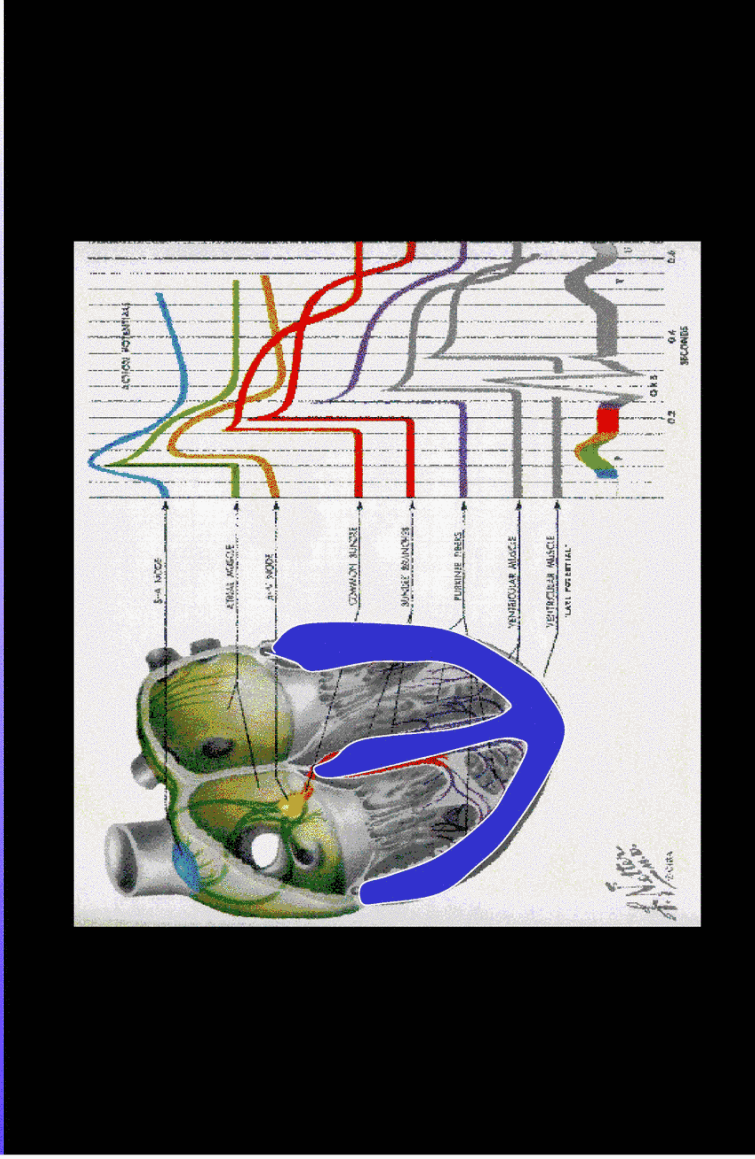
*Peters et al. Circ 1997;95:998*

*Peters NS. Clin Science 1996;90:447*

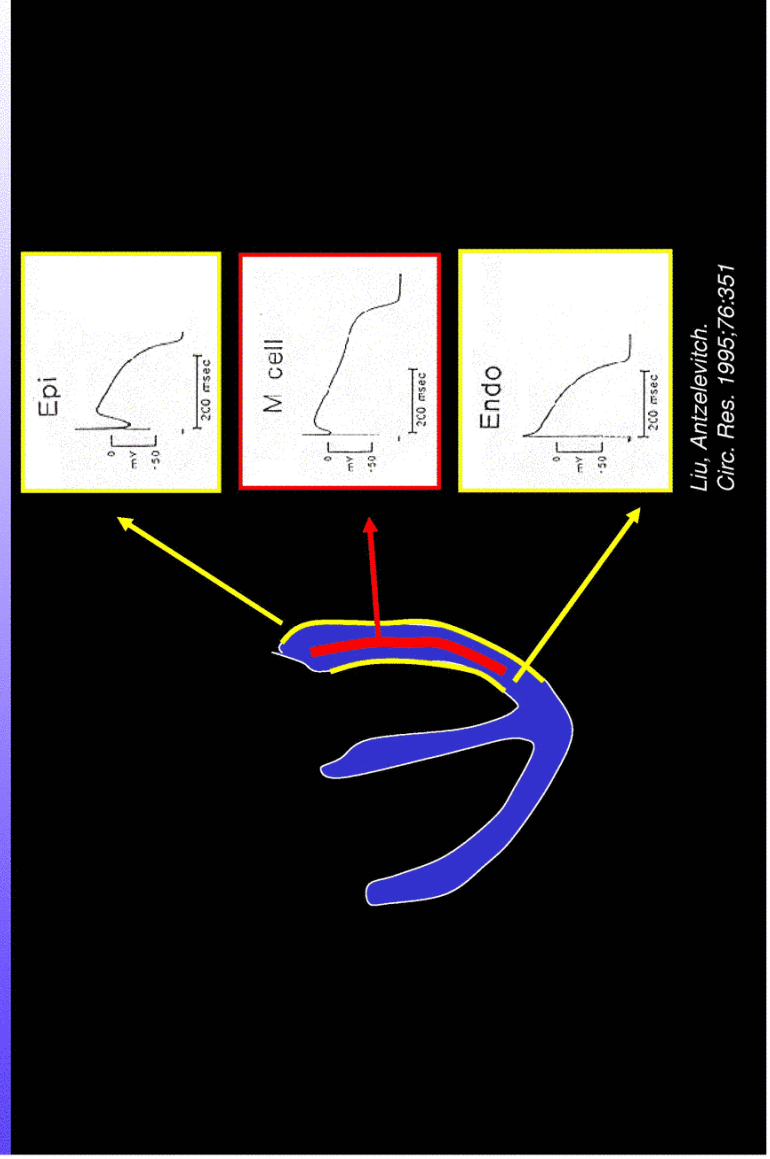
## Electrophysiological heterogeneities underlying arrhythmogenesis



# Electrophysiological Heterogeneity



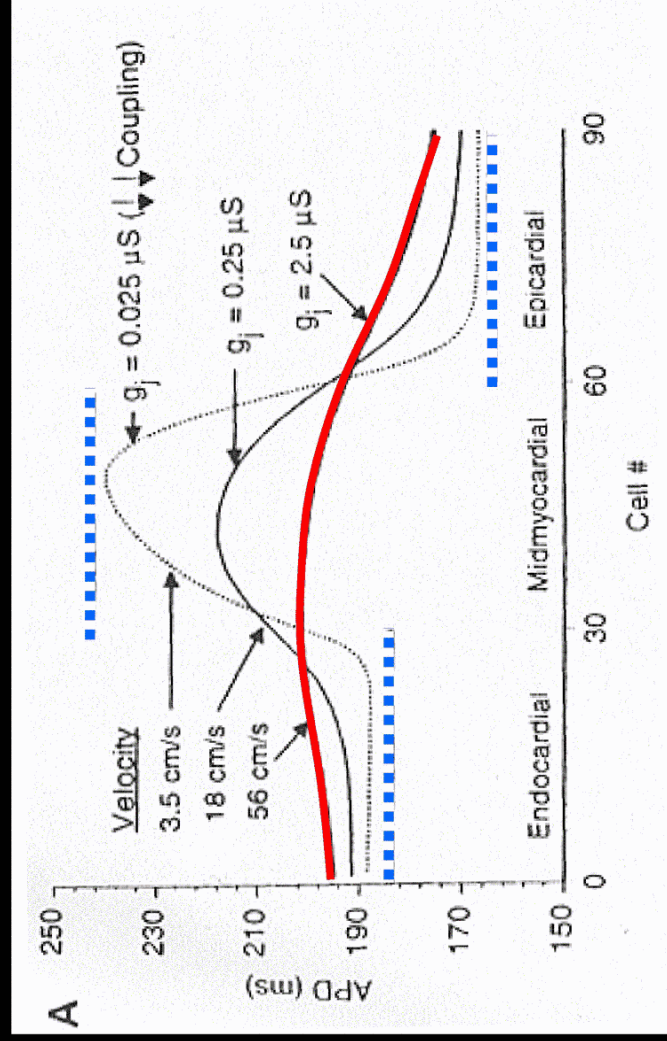
# Transmural Electrical Heterogeneities



## Transmural Heterogeneity in the Heart?



Viswanathan, Shaw, and Rudy 1999



## HYPOTHESIS



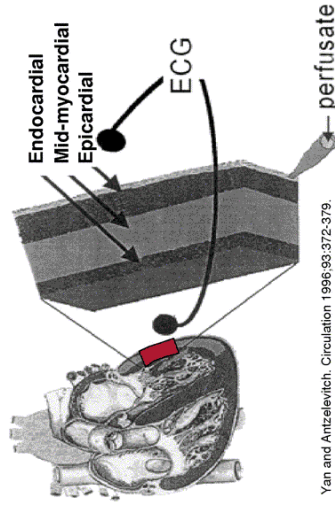
*What is mechanism of pathophysiological heterogeneities in the heart?*

- Spatial inhomogeneities between cells in expression or function of ion channels
- Impaired intercellular coupling between cells.
- Repolarization alternans (inhomogeneities in Ca cycling proteins?)

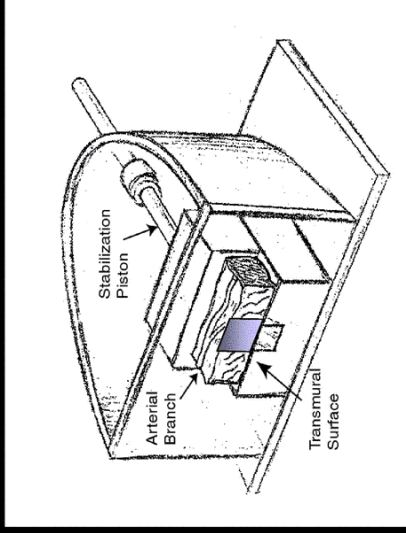
# Transmural Optical Mapping



Arterially Perfused Left Ventricular Wedge

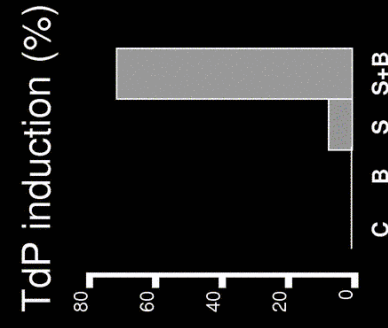
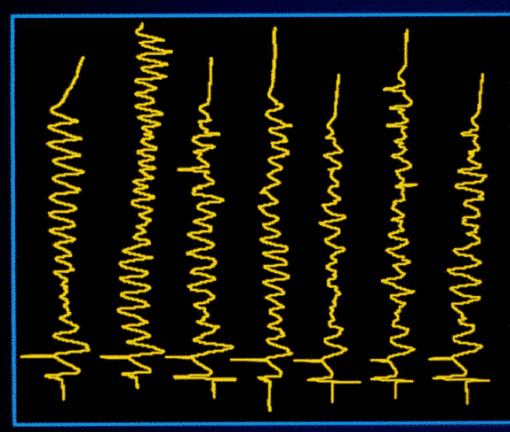


Yan and Antzelevitch, Circulation 1996;93:372-379.



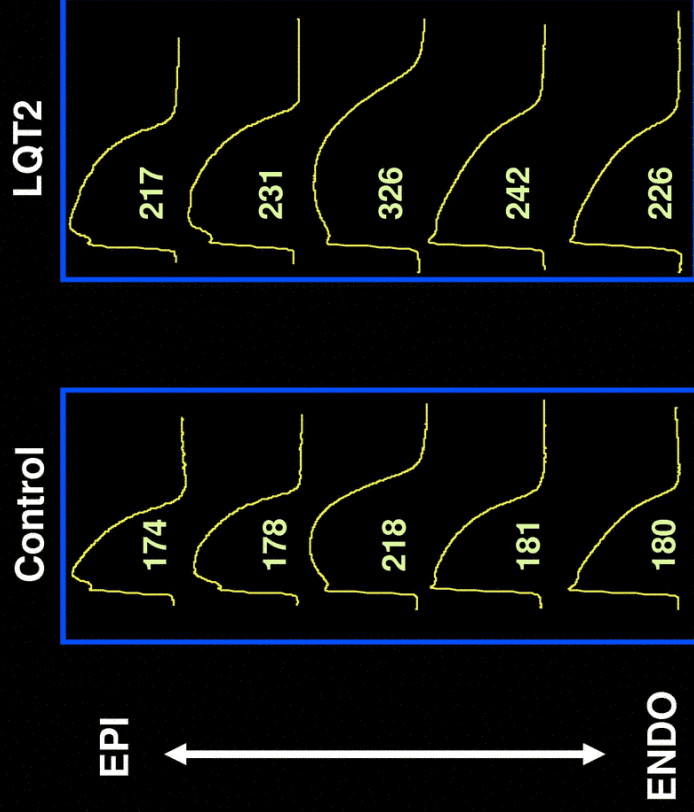
- 256 recording sites
- Resolutions:
  - 0.5 mV voltage
  - 0.5 ms temporal
  - 0.5-1.0 mm spatial

# Torsades de Points in wedge preparation



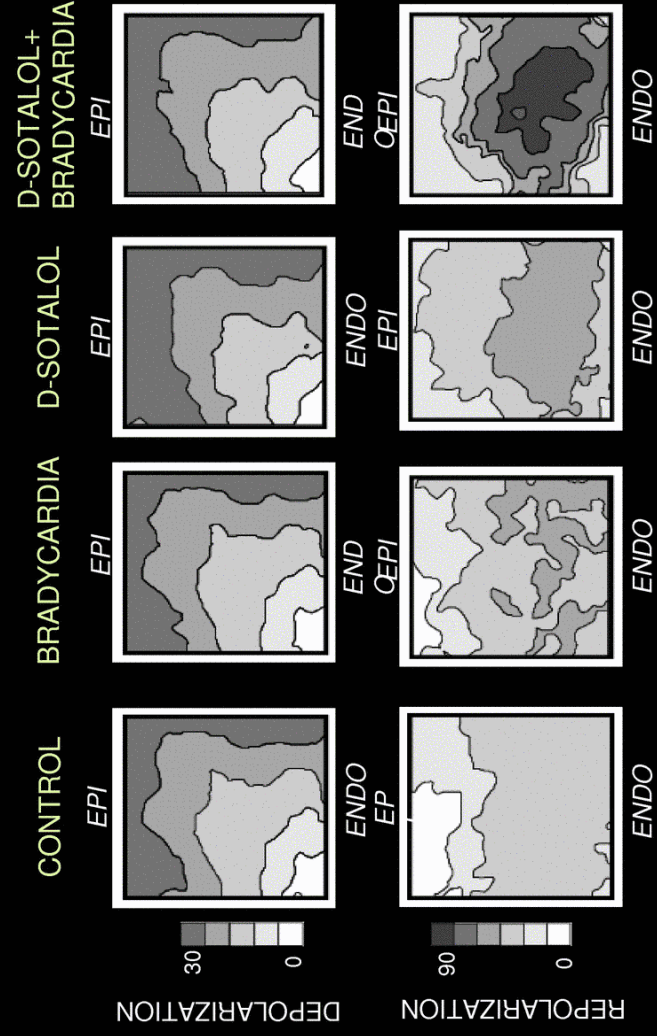


# Transmural Heterogeneities



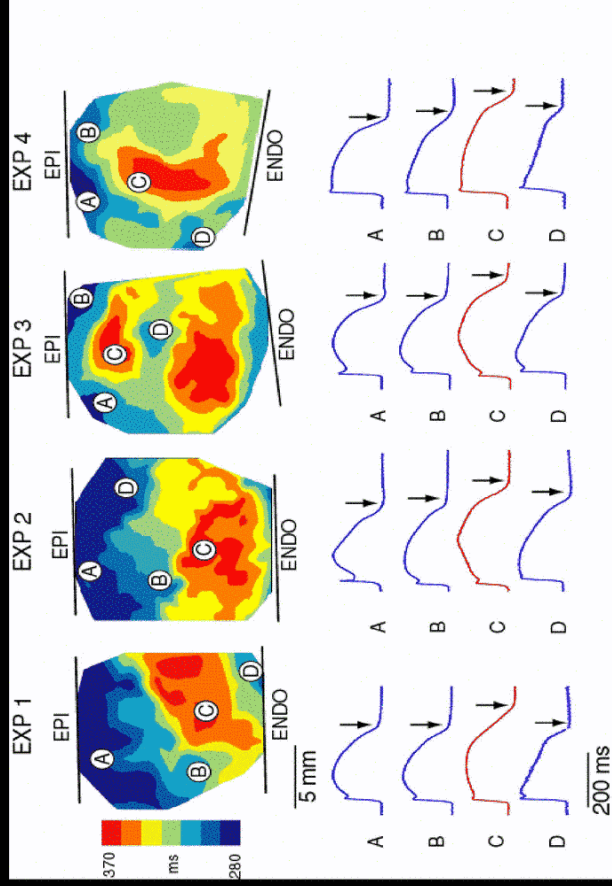
Akar et al. *Circulation* 2002;105:1247

## Substrate for Torsades de Points in LQT2 model



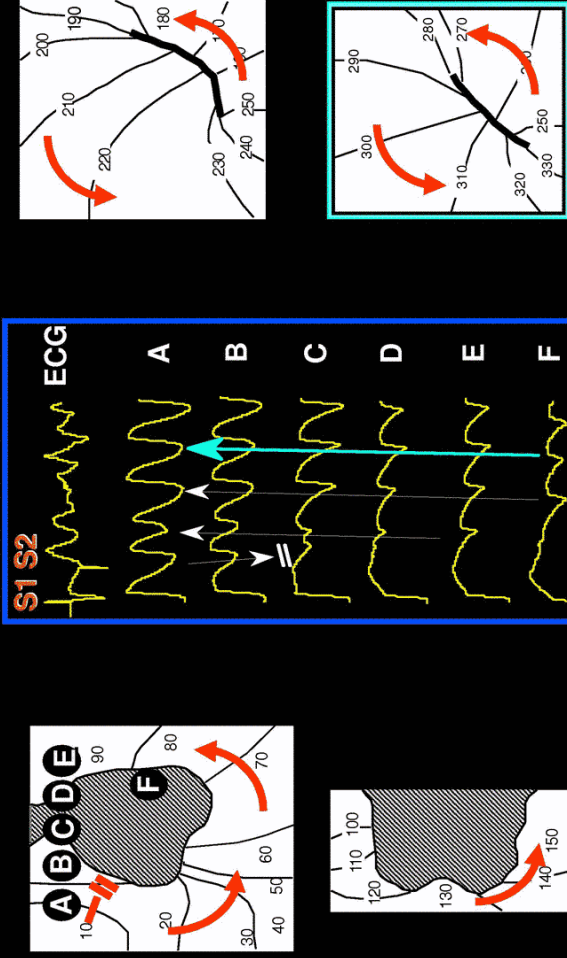
Akar et al. *Circulation* 2002;105:1247

# M CELL TOPOGRAPHY



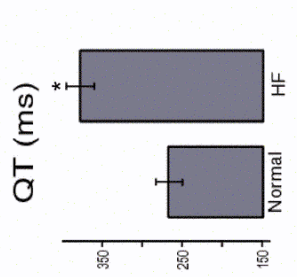
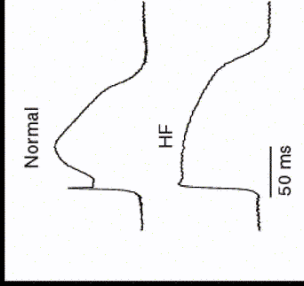
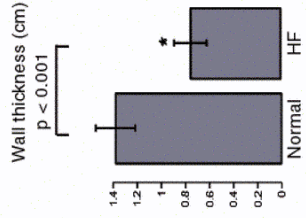
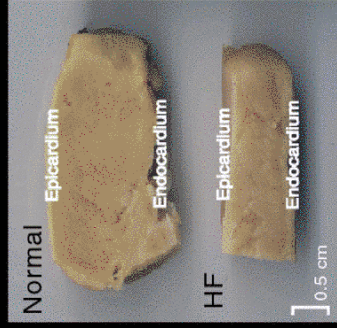
Akar et al. *Circulation* 2002;105:1247

# Transmural reentry underlies Torsades de Pointes



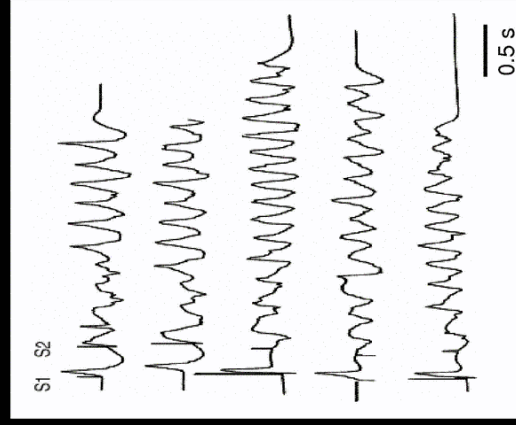
Akar et al. *Circulation* 2002;105:1247

## Canine Wedge Model of Heart Failure



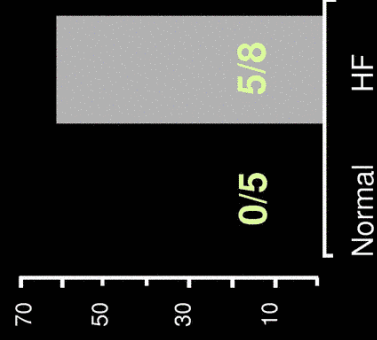
Akar & Rosenbaum.

## Polymorphic VT in Heart Failure

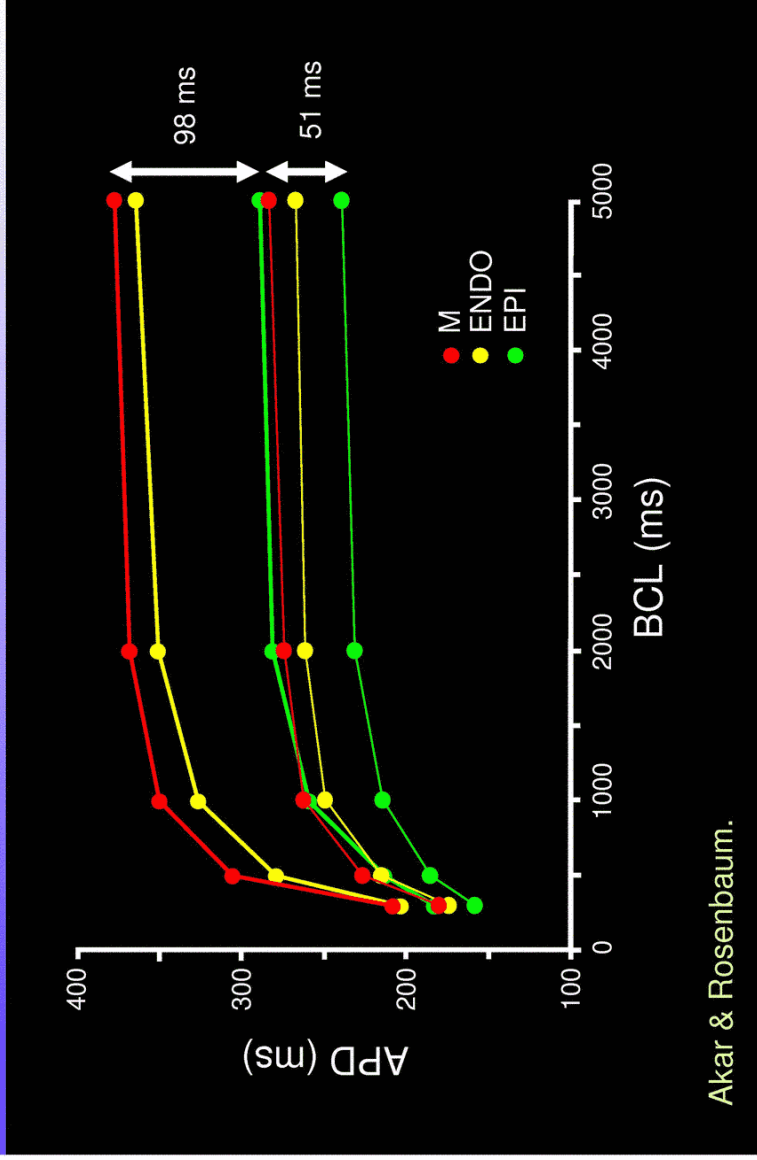


Average cycle length =  $134 \pm 11$  ms

Polymorphic VT  
Induction Rate (%)

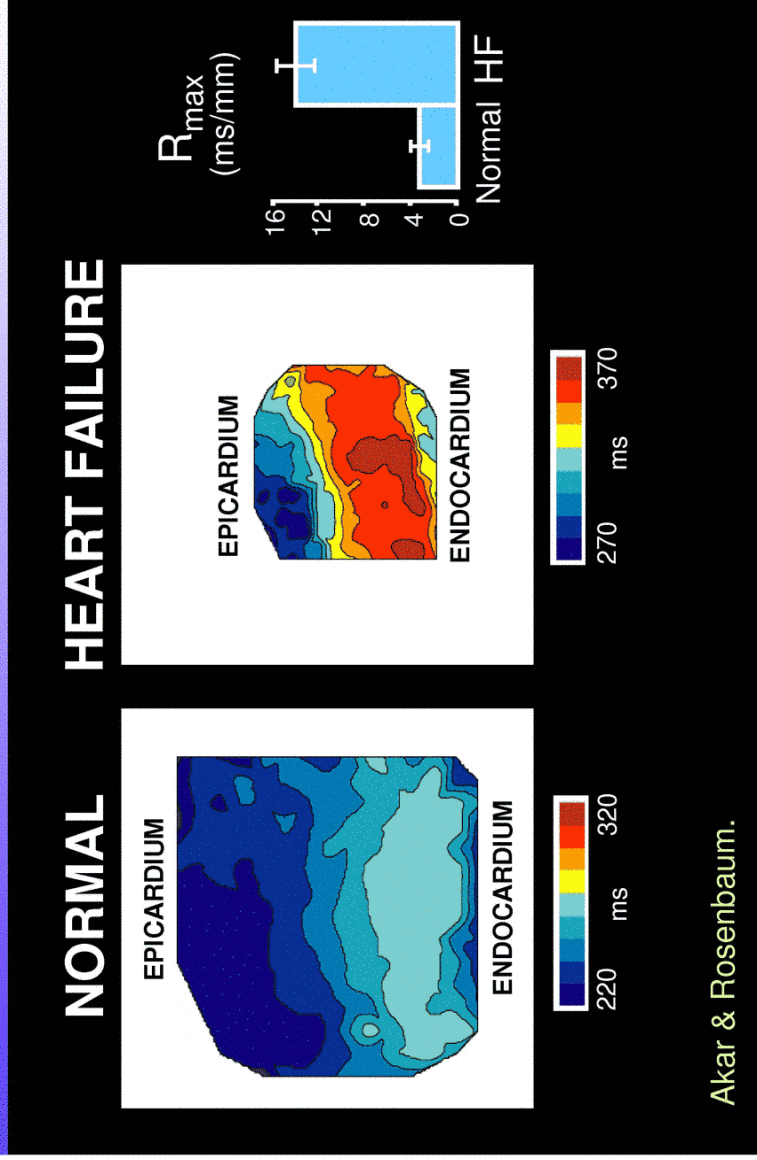


# Rate Adaptation of APD



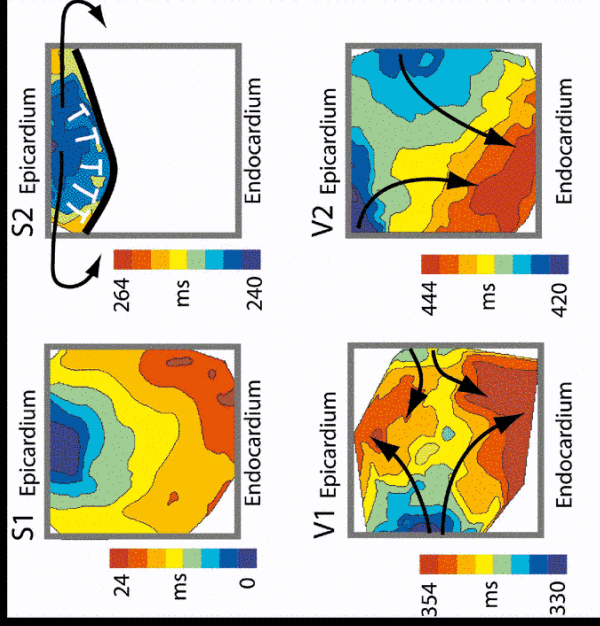
Akar & Rosenbaum.

# APD Topography in Heart Failure

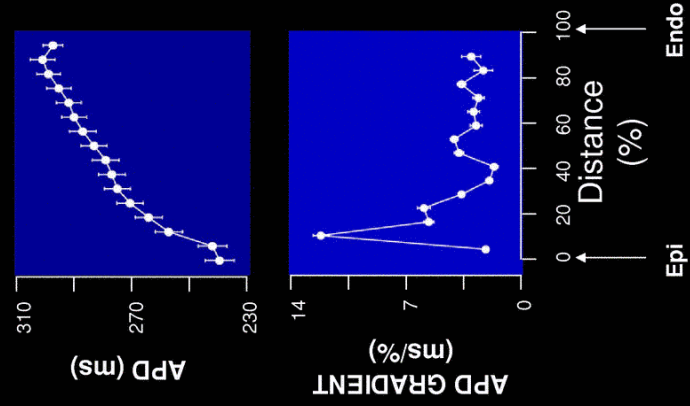


Akar & Rosenbaum.

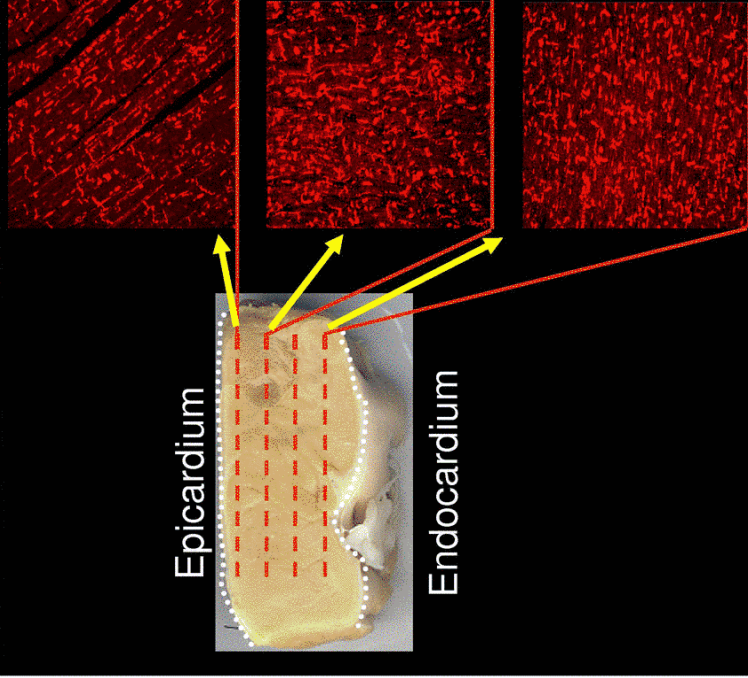
# Arrhythmogenesis in heart failure



# Cx43 Expression Patterns Underlie Transmural Dispersion in Heart Failure

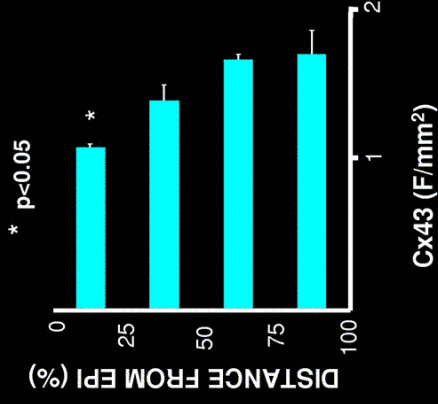


## High resolution quantification of gap junction expression and function

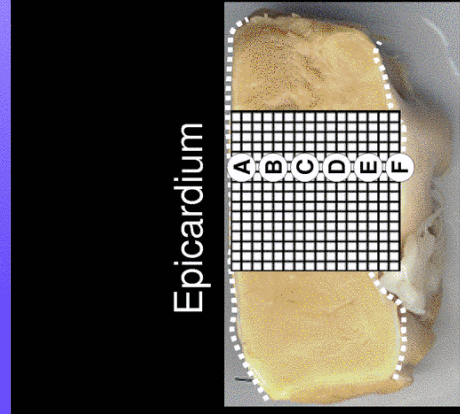


Epicardium

Endocardium

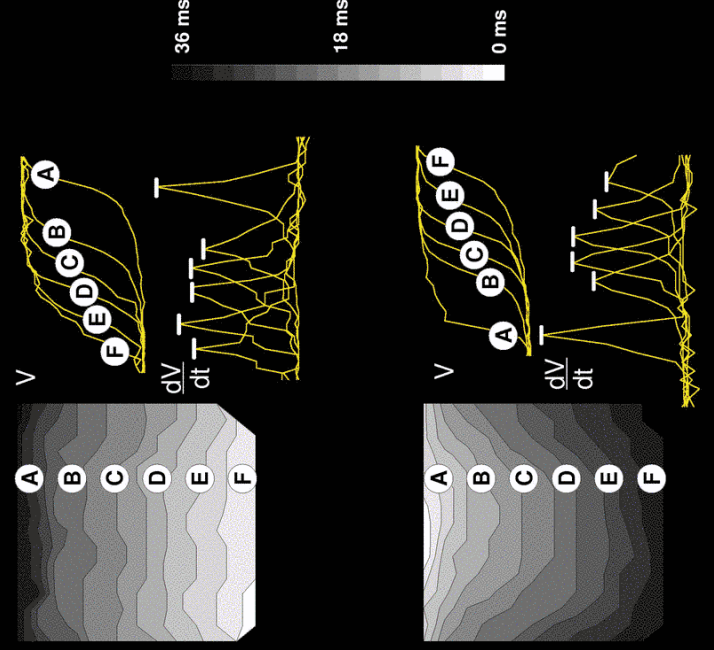


## Transmural Conduction Velocity

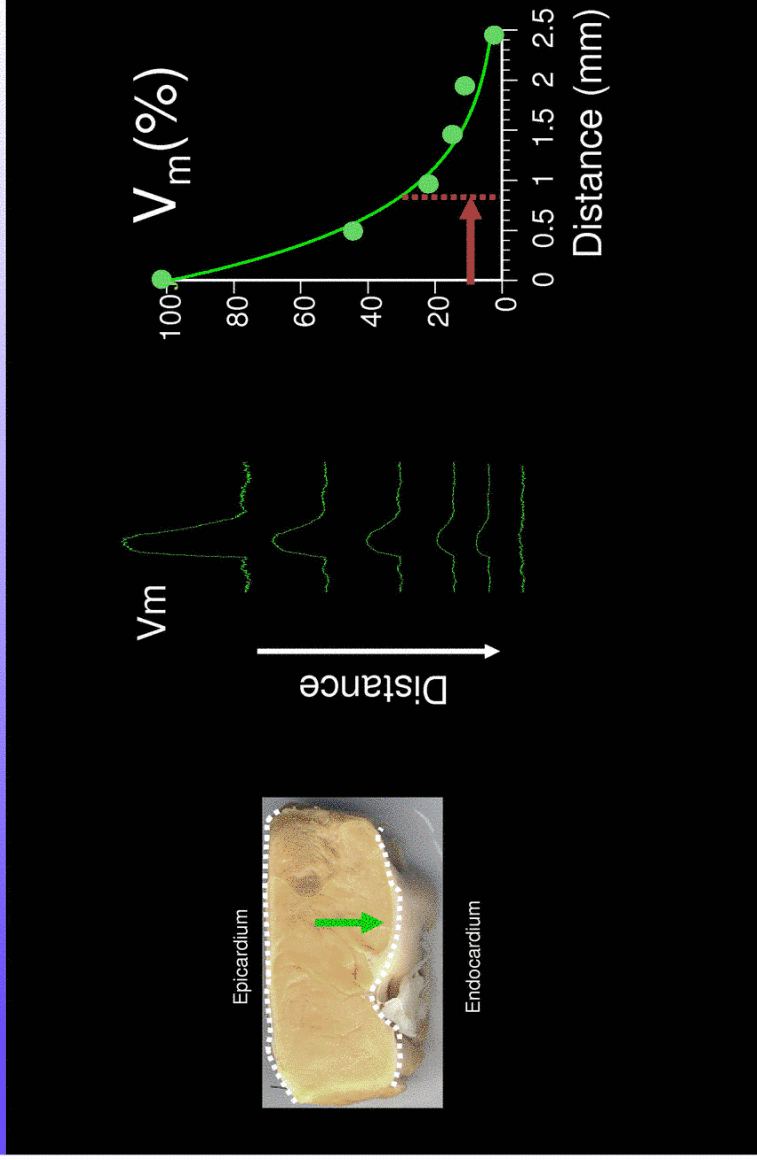


Epicardium

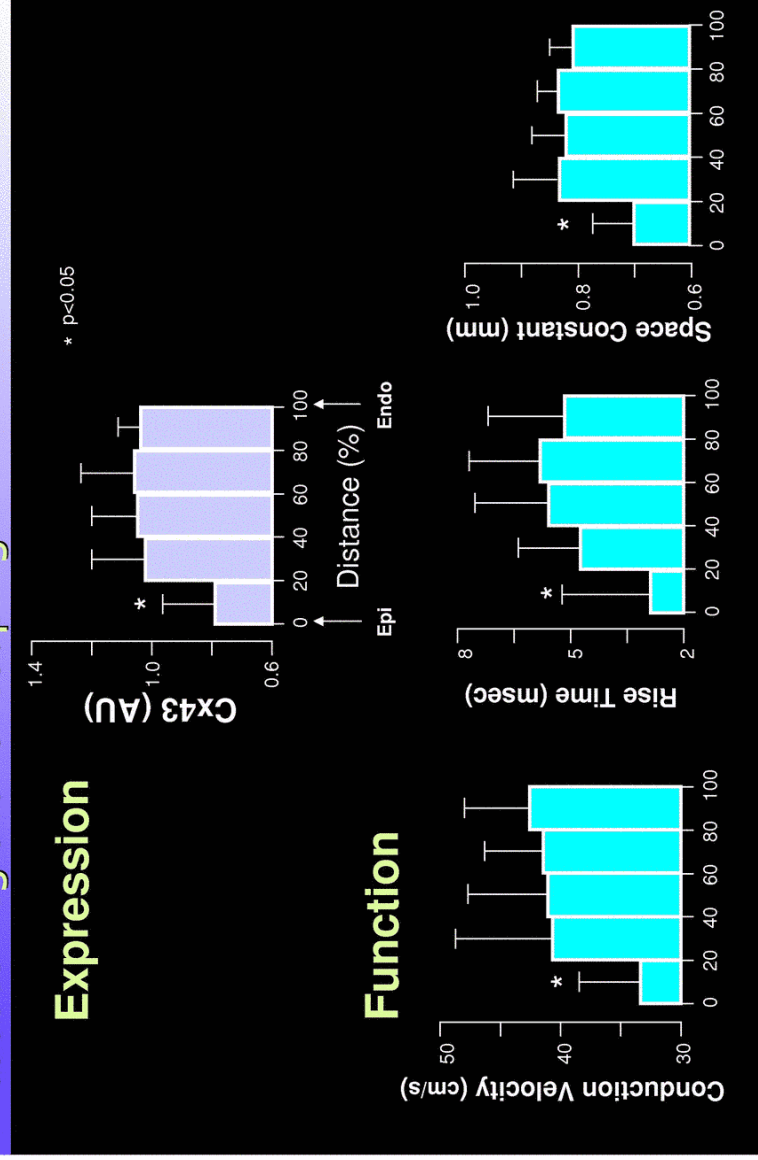
Endocardium



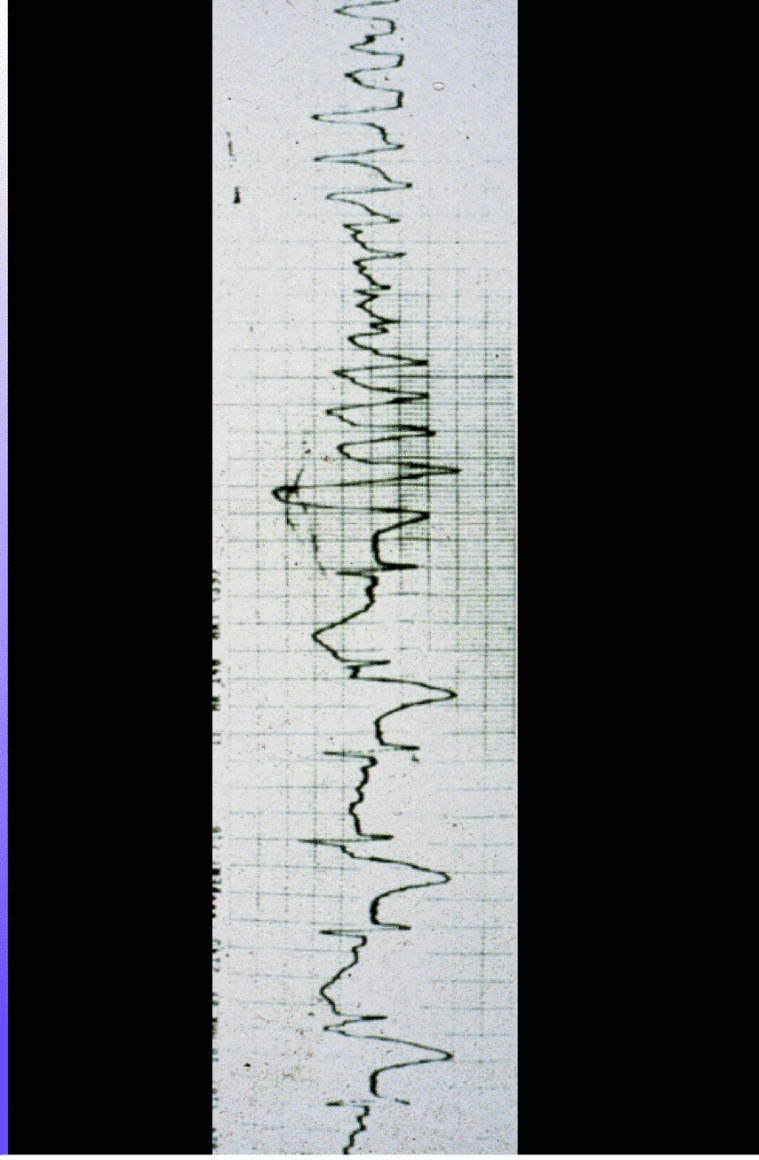
## Transmural Space Constant



## Transmural Cx43 Expression Causes Regional Uncoupling



## Natural History Electrical Alternans?



“the presence of the pulsus alternans in a case of myocardial and arterial disease always adds to the gravity of the prognosis.”

“It signifies disease of the heart progressing inevitably to a fatal end; and this is its meaning when present, as it seldom is for a time, in patients whose clinical condition does not suggest serious unsoundness of the heart.”

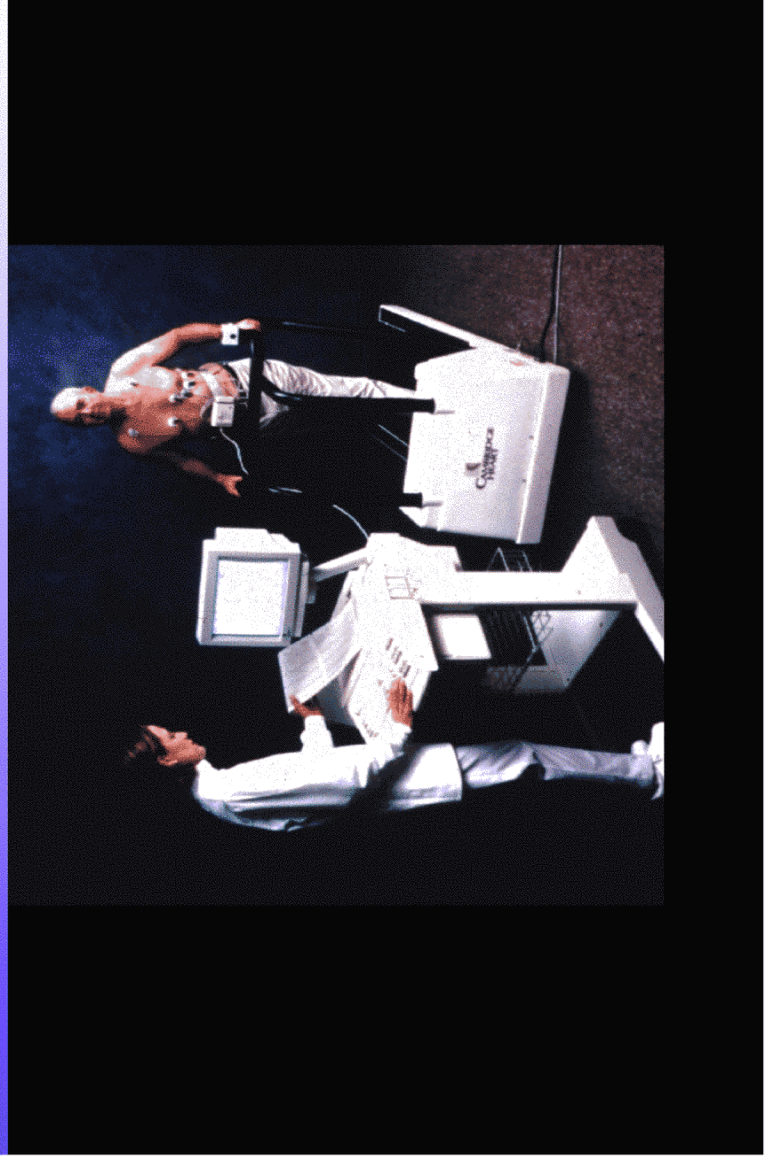
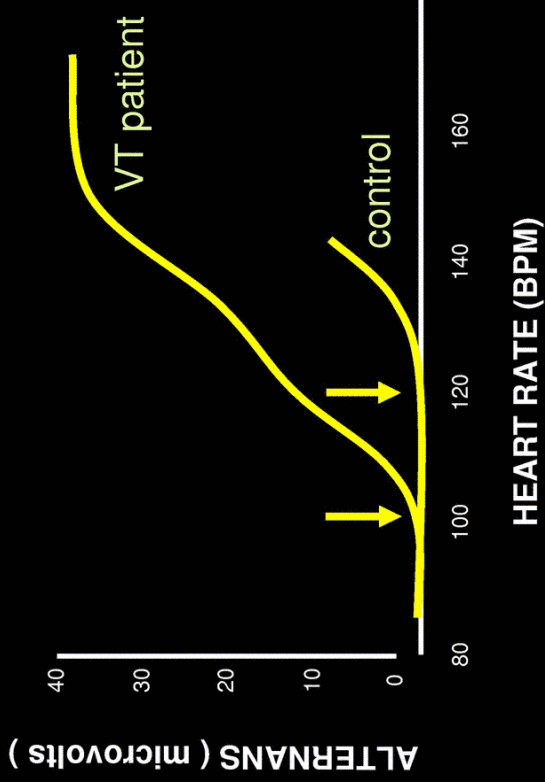




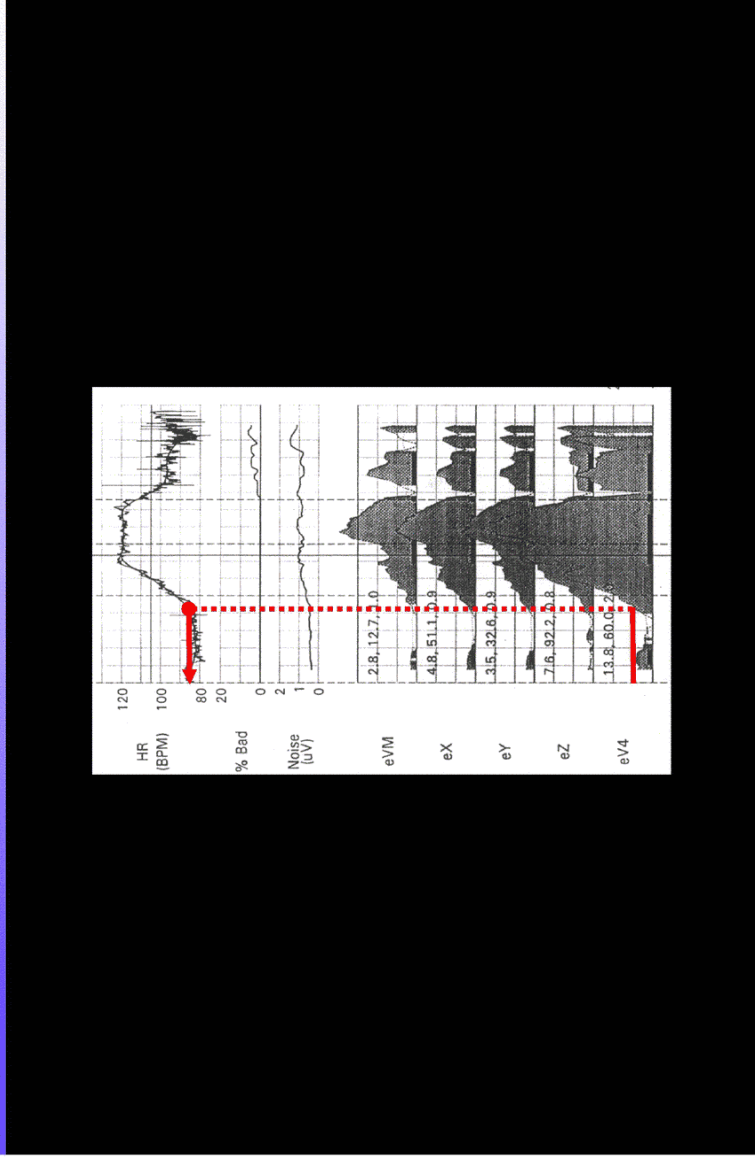
### Heart Rate Dependence of T Wave Alternans



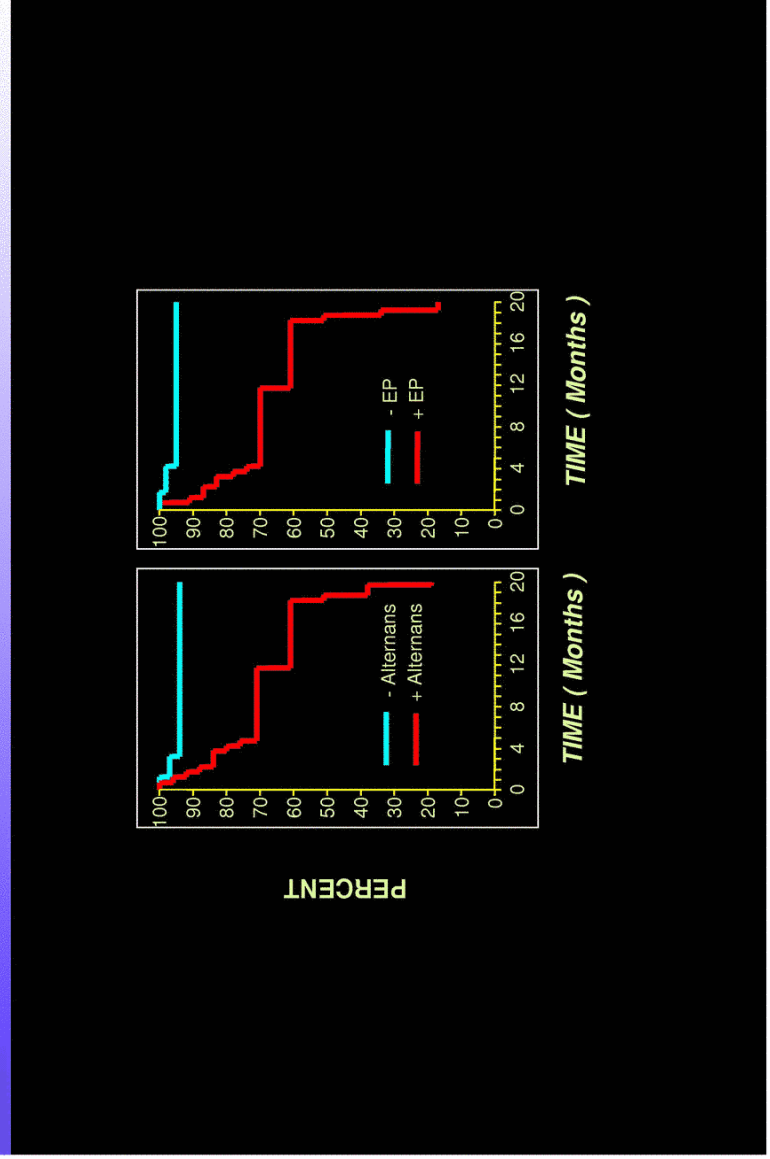
Kaufman E, et al. *Am J Physiol.* 2000;279:H1248-H1255.



68 y/o asymptomatic male with ischemic heart disease, nonsustained VT and a negative EP study.

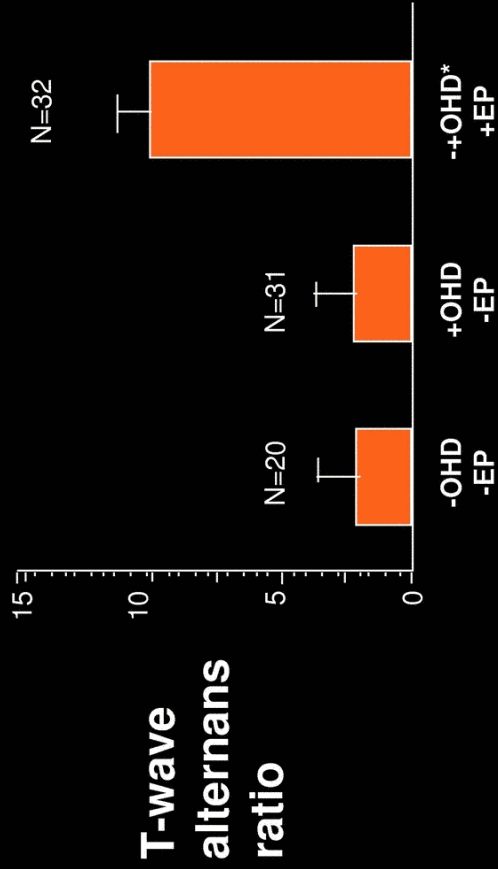


Arrhythmia-Free Survival 1994-330-2336



# T Wave Alternans is a Marker of Electrical Dysfunction

Rosenbaum et al. N Engl J Med 1994;330:235-241



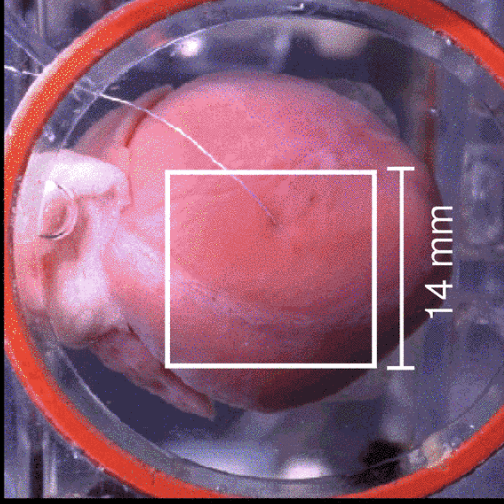
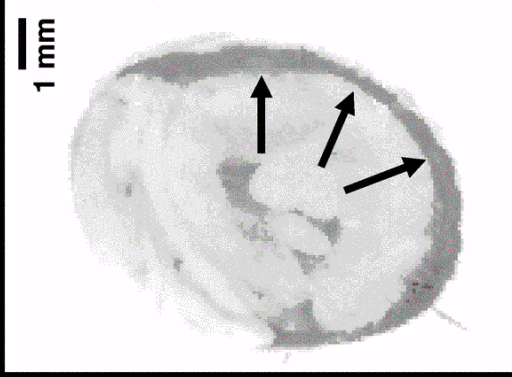
## Clinical Trials on T wave alternans, 2003



Table 1. Overview of the performance of T wave alternans analysis for risk assessment of arrhythmic events.

Patient characteristics	Results of TWA (%)				pV of inductibility at EPS				Follow up			Independent predictor of events		pV of event at follow up			
	N	Population, Heart disease	LVEF (%)	Indetermin	+Twa	-Twa	Indetermin	excluded	PPV (%)	NPV (%)	RR	Duration (yr)	Event (%)	Event (%)	Independent predictor of events	PPV (%)	NPV (%)
Rosenbaum et al 1994 <sup>13</sup>	68	1° & 2° 66% CAD	40		69	31		excluded	76	88	5.2	VTE	20	20	+TWA, +EPS	81	94
Ernst et al 1997 <sup>15</sup>	51	1° & 2° 40% CAD	55		48	30	18		67	92	8.7	None	NA	NA	NA	NA	NA
Helmreich et al 1998 <sup>16</sup>	95	2° 75% CAD	36		41	30	29		NA	NA	NA	1.5 VTE	43	43	+TWA	65	80
Gold et al 2000 <sup>17</sup>	313	1° & 2° 41% CAD	44		31	45	24		43	93	5.7	1.2- VTE	8	8	+TWA, +EPS	19	98
Beeda et al 2000 <sup>18</sup>	142	1° 100% CAD	49		35	37	12		NA	NA	NA	1 VTE	15	15	+TWA, +SAJECG, LVEF	28	98
Adachi et al 2001 <sup>19</sup>	82	1° 100% DCM	44		37	41	22		NA	NA	NA	2 VTE	12	12	+TWA, LVEF	30	97
Tapanainen et al 2001 <sup>20</sup>	379	1° 100% CAD	45		15	38	32% (no test 13%)		NA	NA	NA	2 Mortality	7	7	Incomplete TWA, +SAJECG	0	96
Klingenhöfen et al 2001 <sup>21</sup>	65	1° & 2° 70% CAD	37		89	11	17		NA	NA	NA	NA	NA	NA	NA	NA	NA
Beeda et al 2002 <sup>18</sup>	850	1° 100% CAD	51		36	52	12		NA	NA	NA	2 VTE	8	8	+TWA, +SAJECG, LVEF	8	99
Kaulba et al 2002 <sup>22</sup>	143	1° & 2° 100% CAD	27		49	26	25		79	45	3	1.5 VTE	35	35	+TWA	45	80
Kaulba et al 2002 <sup>23</sup>	144	1° & 2° 100% CAD	28		49	26	25		NA	NA	NA	1.5 VTE	37	37	+TWA, GRS-0.12	44	76
Kittanen et al 2002 <sup>24</sup>	104	1° 100% DCM	41		44	36	20		NA	NA	NA	2 VTE	14	14	+TWA, LVEF	24	97
Bloomfield et al 2003 <sup>25</sup>	542	1° 47% CAD	<40		30	34	36		NA	NA	NA	2 Mortality	7	7	+TWA	6	99
Sinnamy <sup>25</sup>	164	100% CAD	25		30	34	36		NA	NA	NA	4 Mortality	4	4	+TWA	13	100

# The Guinea Pig Model of Pacing Induced T Wave Alternans

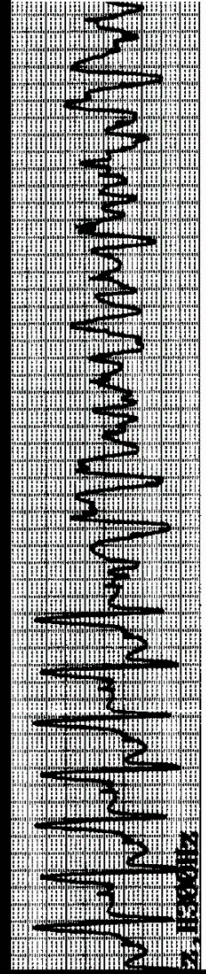


cross-section of  
ventricle

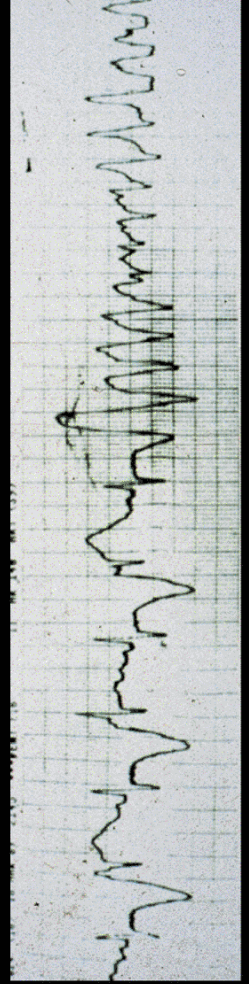
# ALTERNANS PRECEDING VF



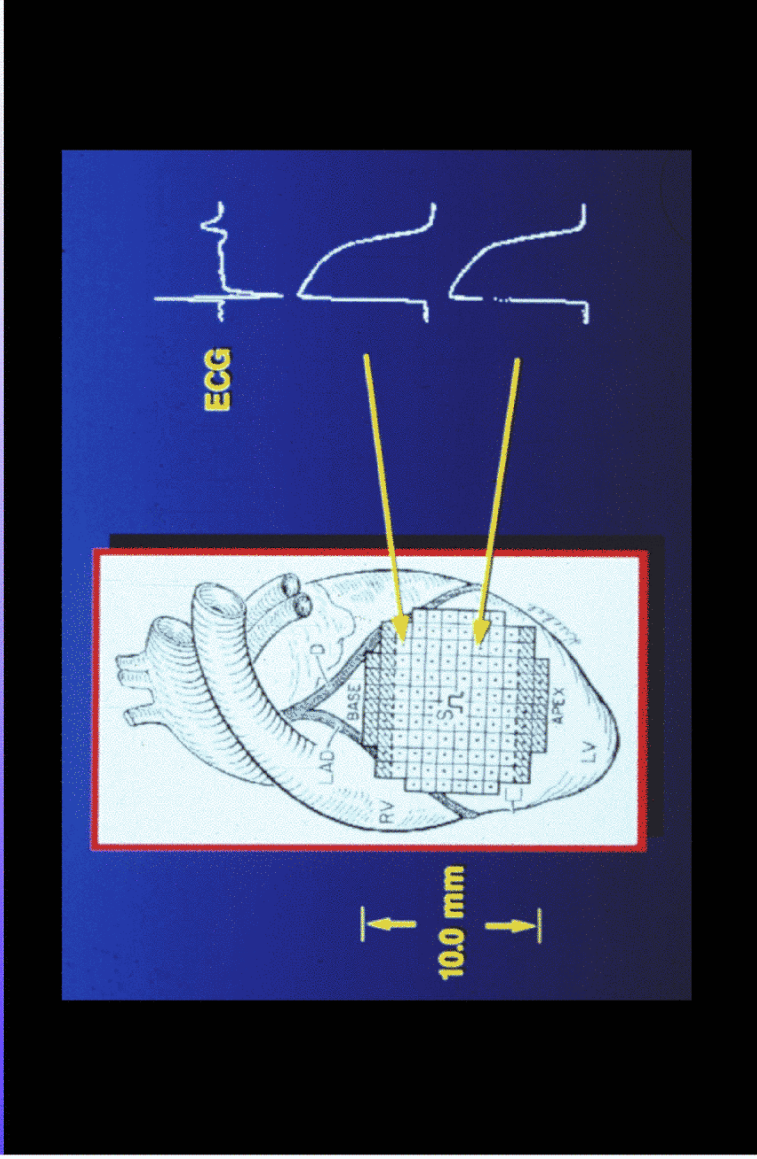
Guinea pig



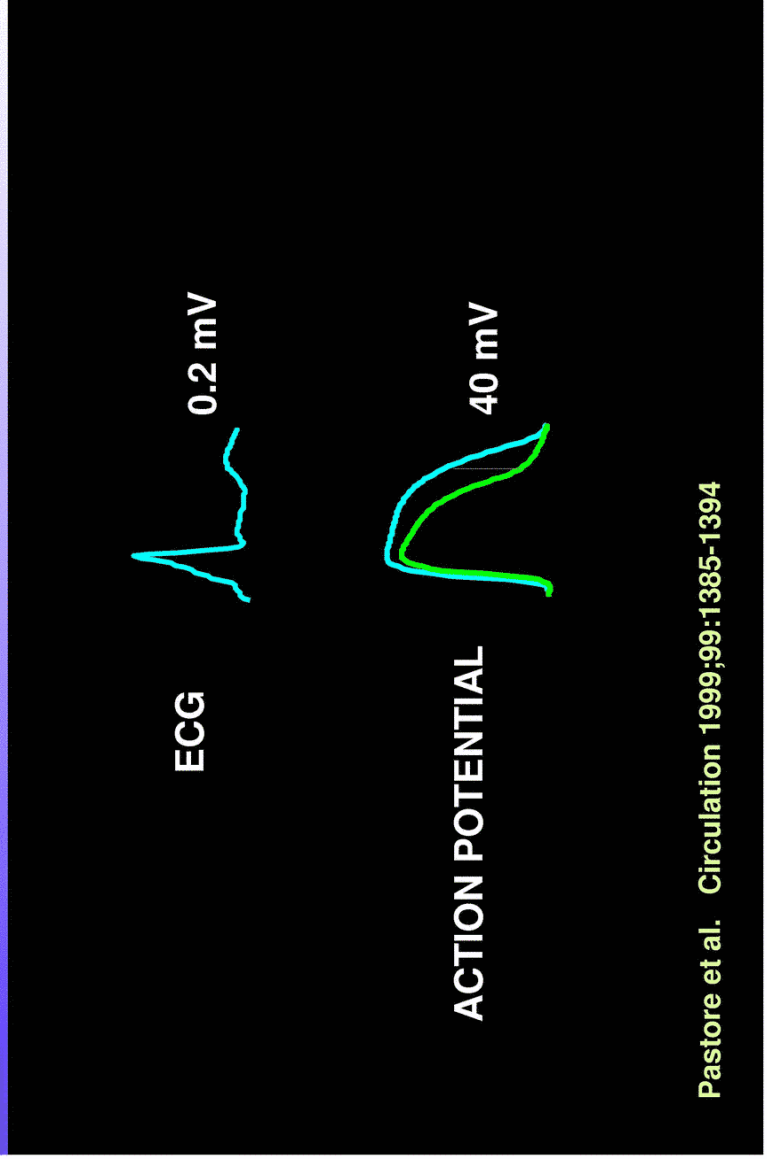
Patient



# Optical Action Potentials

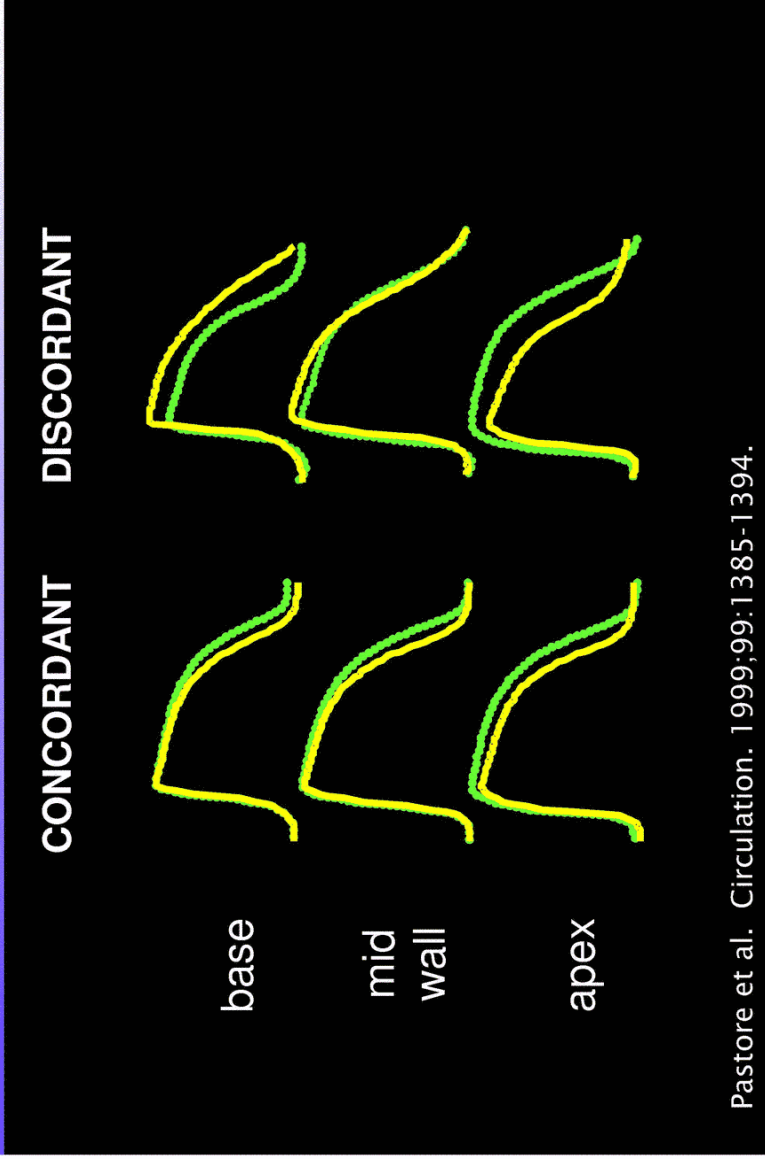


# Cellular Basis for T Wave Alternans



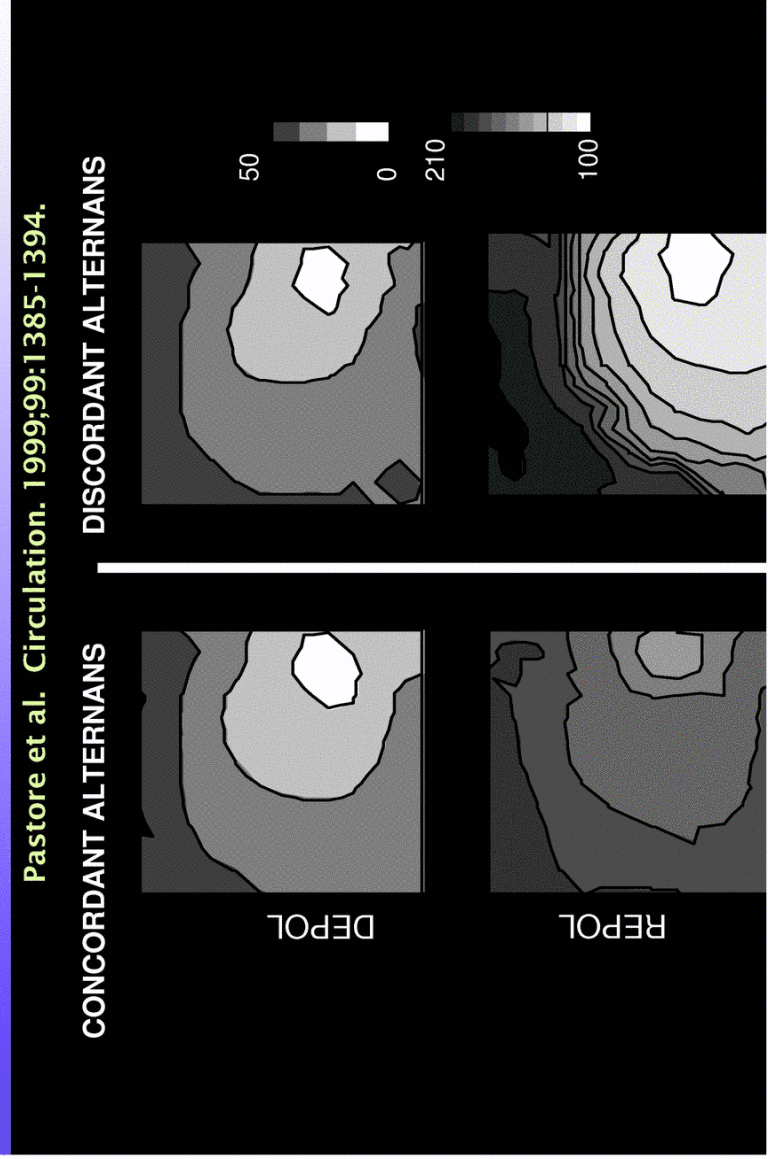
Pastore et al. Circulation 1999;99:1385-1394

# Concordant vs discordant alternans



Pastore et al. Circulation. 1999;99:1385-1394.

# Effect Of Discordant Alternans On Repolarization

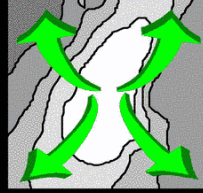


Pastore et al. Circulation. 1999;99:1385-1394.

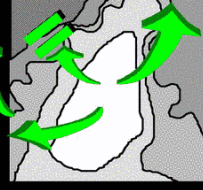
## Alternans-Induced VF

Pastore et al. *Circulation*. 1999;99:1385-1394.

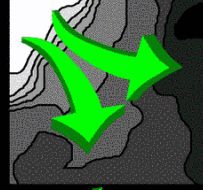
VPB



DEPOLARIZATION

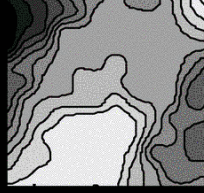


VPB



VF

S1

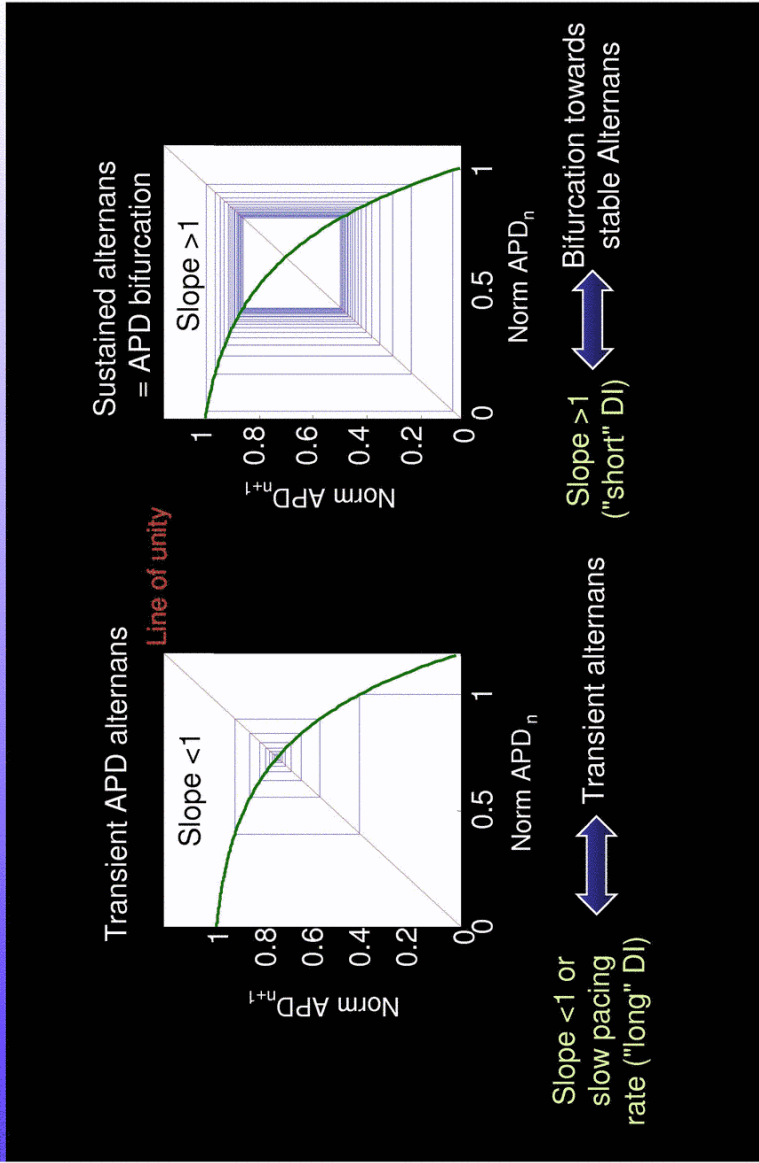


REPOLARIZATION

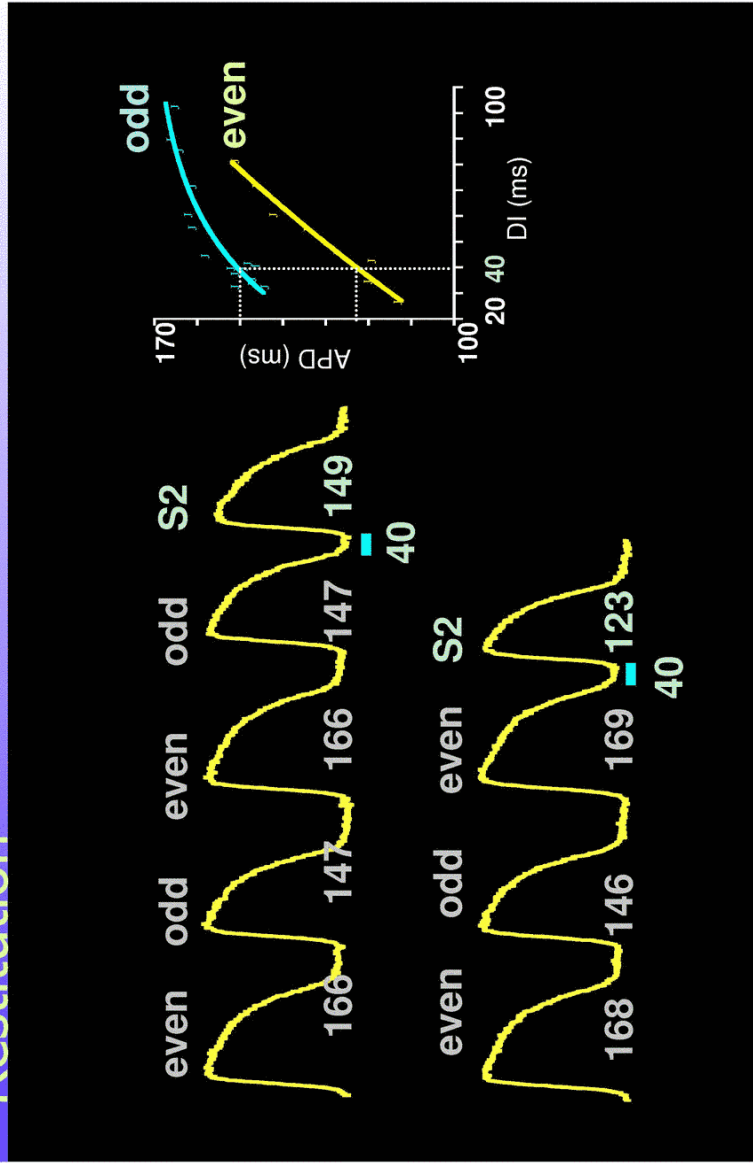
## Some key questions

1. What is the mechanism responsible for repolarization alternans of individual myocytes?
  - restitution hypothesis
  - calcium cycling hypothesis
2. What is the mechanism responsible for discordant alternans between myocytes?
  - restitution of conduction hypothesis
  - intercellular uncoupling

## Role of Steepness of APD Restitution in Alternans

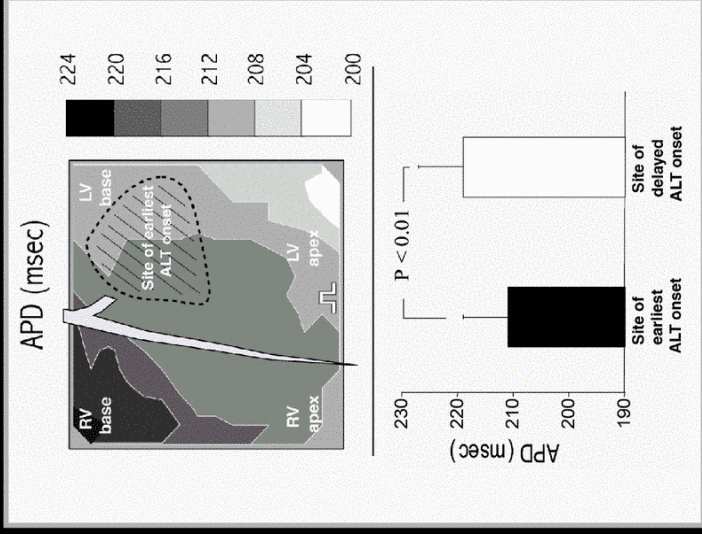


## Effect Of Alternans On Restitution

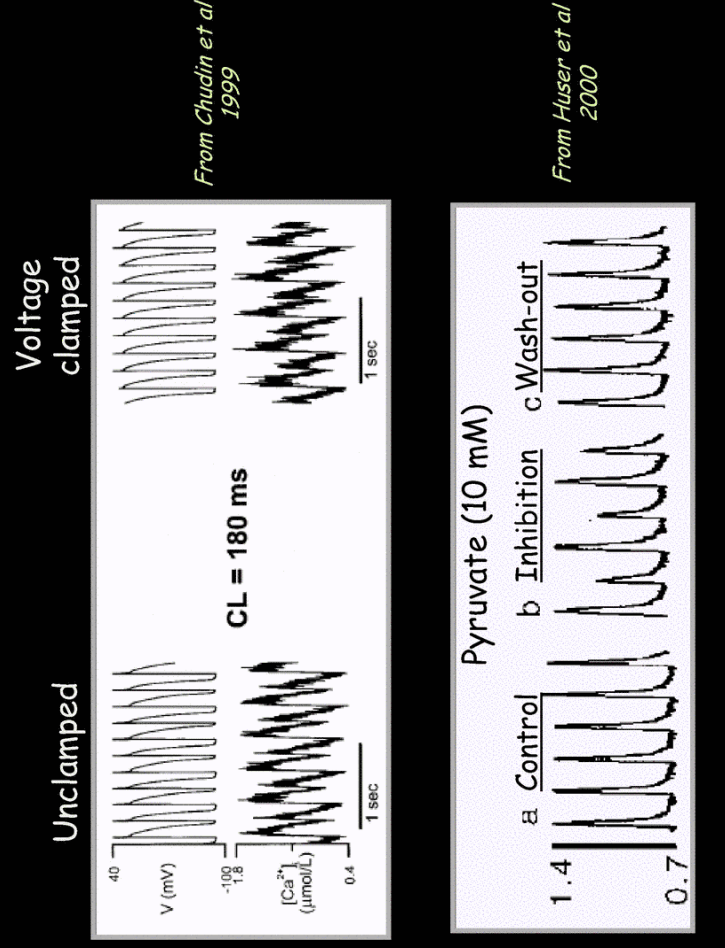




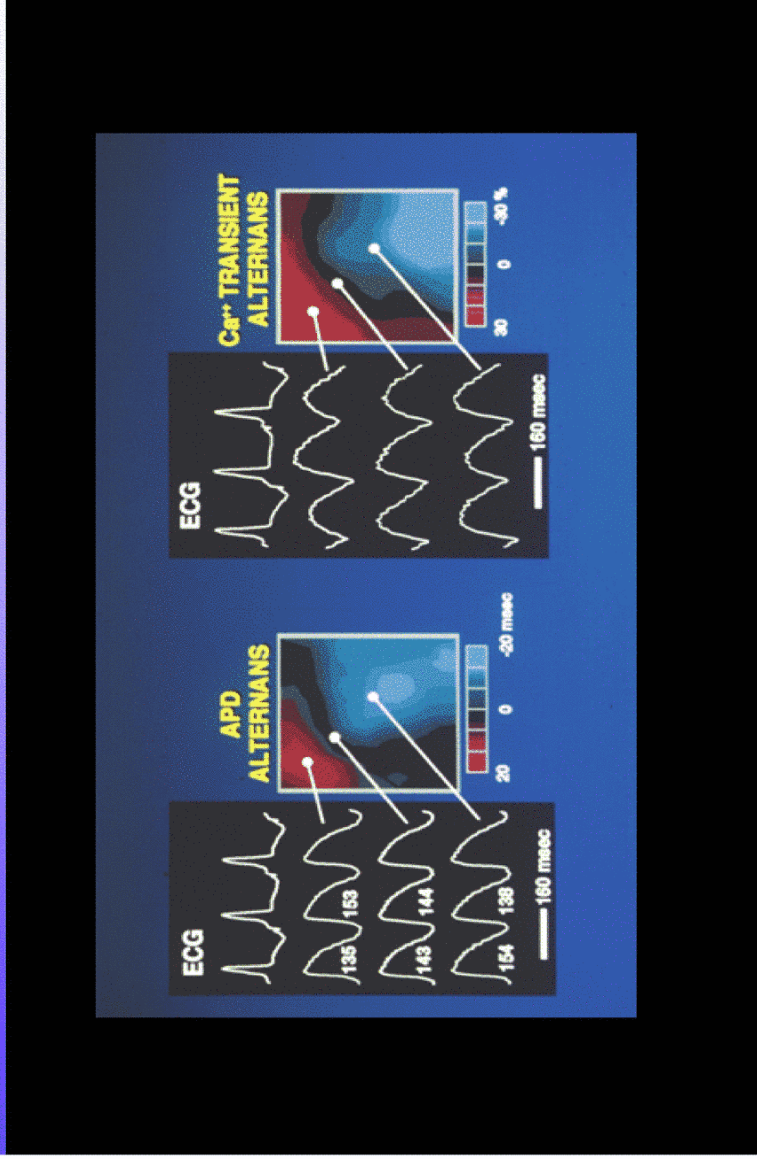
Onset of APD Alternans Does not Occur Where APD is Longest



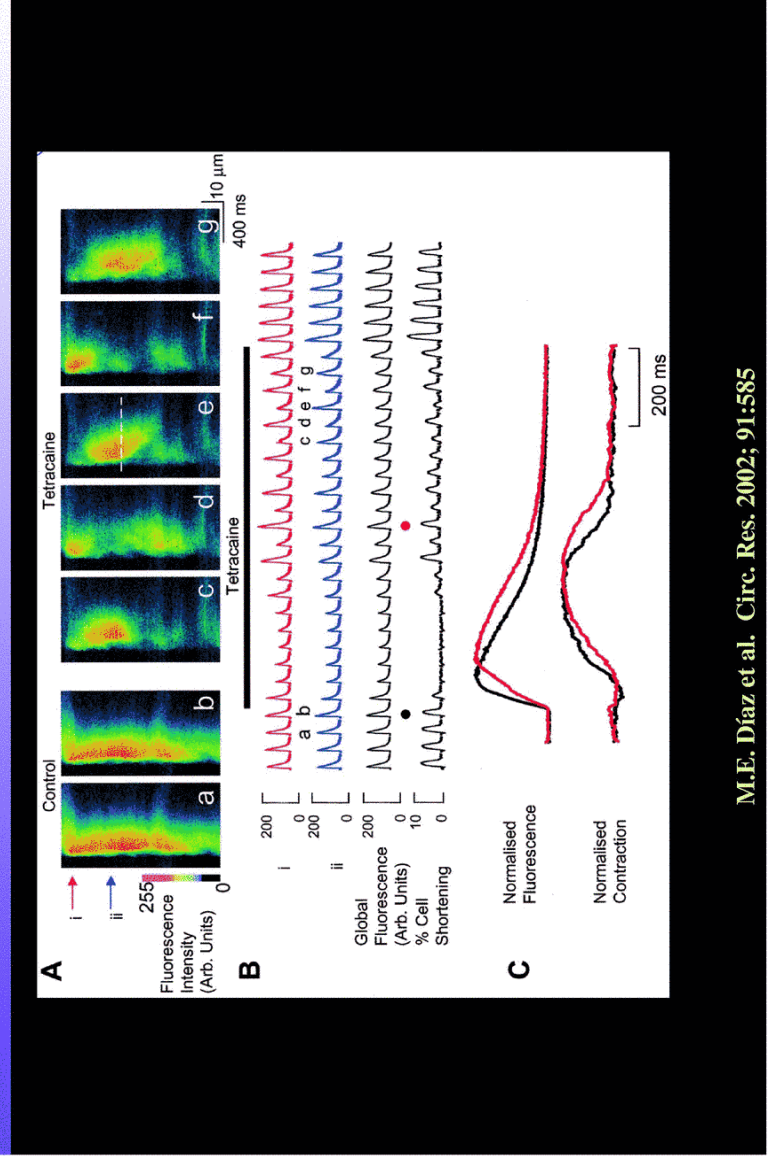
Role of  $Ca^{2+}$  cycling in APD alternans



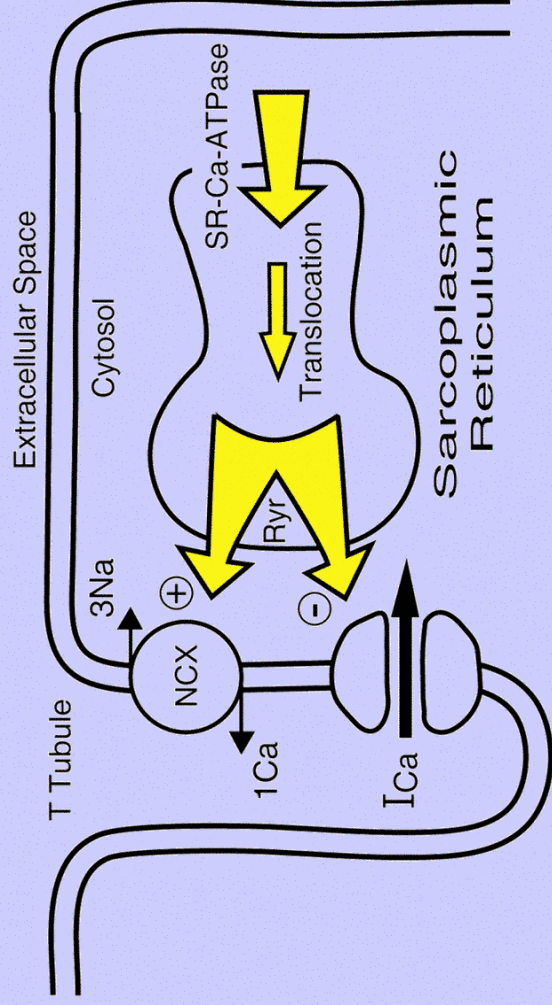
# Discordant Alternans



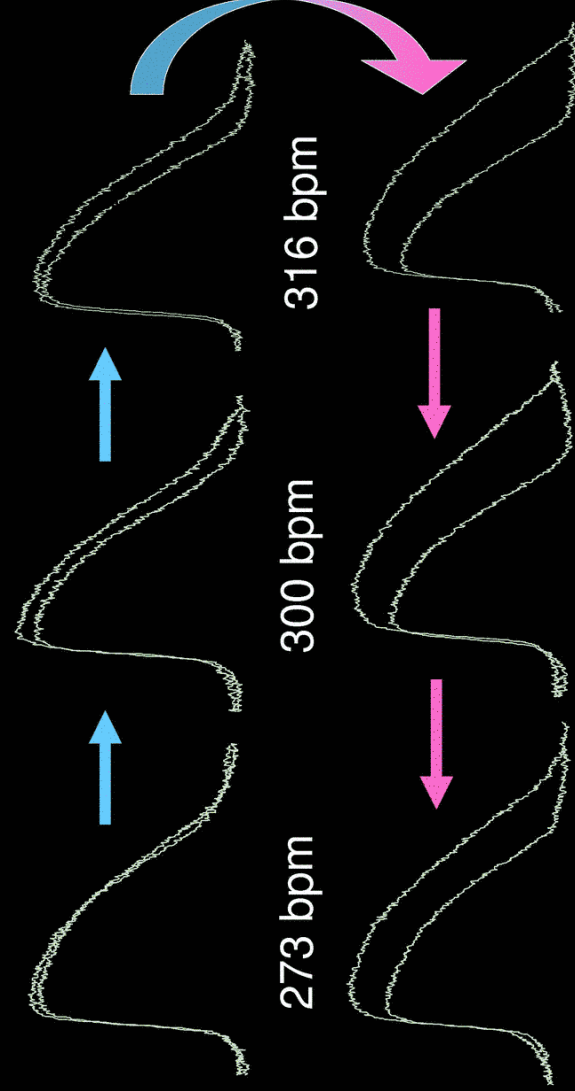
# Reduced RyR Open Probability Induces Regional Alternans



## Calcium Homeostasis



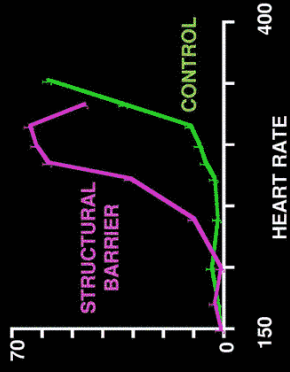
## Cardiac Memory in Cellular Alternans



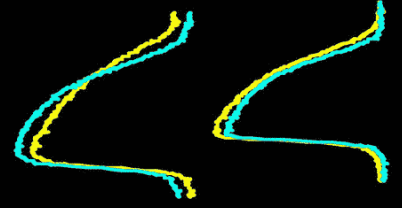
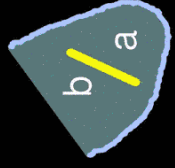
# Role of intercellular uncoupling



ACTION POTENTIAL ALTERNANS (mV)



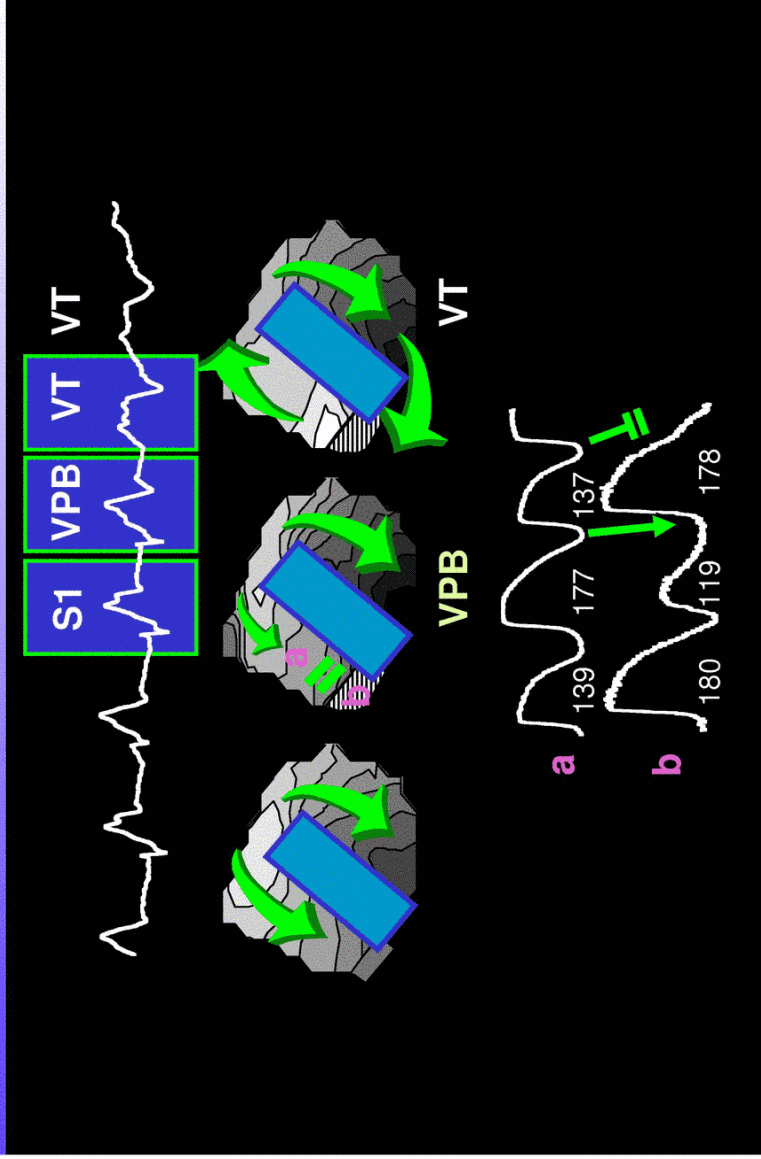
Pastore & Rosenbaum. *Circ.Res.* 2000



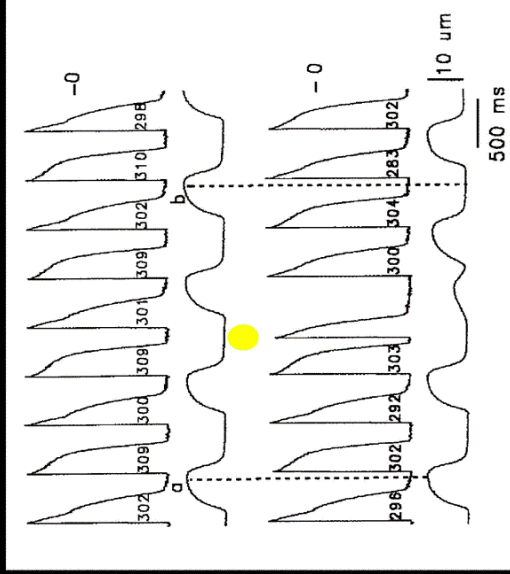
a

b

Pastore & Rosenbaum. *Circ.Res.* 2000;87:1157-1163



## Phase-resetting Of Alternans



Rubenstein DS, Lipsius SL. *Circulation* 1995;91:214

## Mechanism Of Discordant Alternans



Qu Z, Garfinkel A, Chen PS, Weiss, JN. *Circulation* 2000;102:1664-70

### Appendix

#### Mechanism of Discordant Alternans

Assume APD and CV restitution are valid in a spatially uniform system:

$$(5) \quad APD_{n+1}(r) = [D]I_n(r) = F[CL_n(r) - APD_n(r)],$$

$$CV_{n+1}(r) = g[D]I_n(r).$$

In Equation 5,  $CL_n(r)$  can be expressed as

$$(6) \quad CL_n(r) = PCL + \int_0^r \frac{dr'}{CV_{n+1}(r')} - \int_0^r \frac{dr'}{CV_n(r')}$$

$$= PCL + \int_0^r \frac{CV_n(r') - CV_{n+1}(r')}{CV_{n+1}(r') \cdot CV_n(r')} dr'$$

$$= PCL + \int_0^r \frac{-\Delta CV(r')}{CV_{n+1}(r') \cdot CV_n(r')} dr'$$

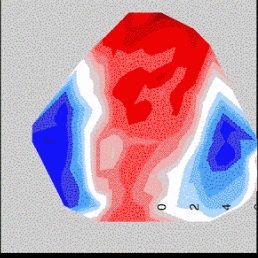
$$= PCL + \Delta CL_n(r)$$

$$= APD_n(r) + DL_n(r).$$

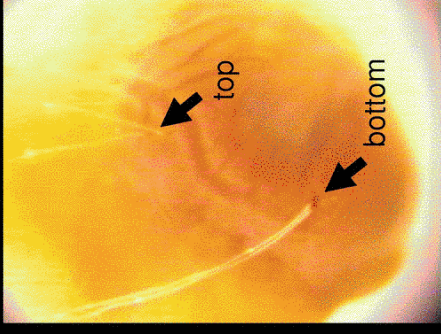
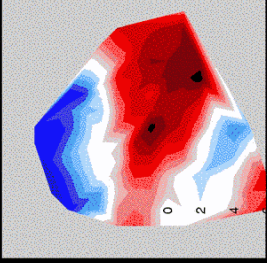
## Dual Pacing Site Experiments



pacing from top



pacing from bottom



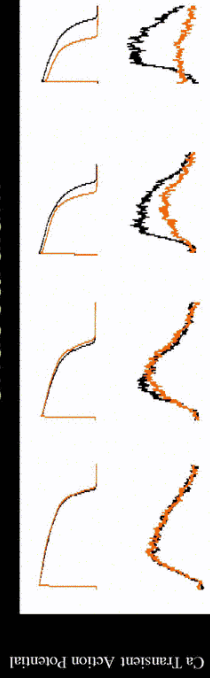
**GP#112**

all at 190 msec

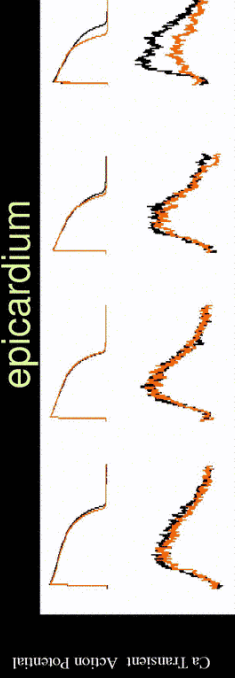
## Calcium cycling alternans



endocardium



epicardium



Pacing rate  
bpm

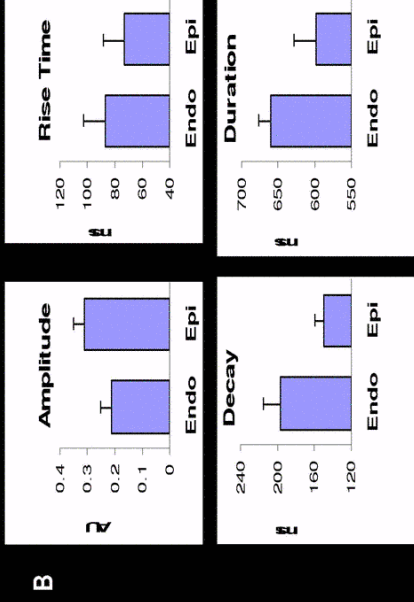
150

120

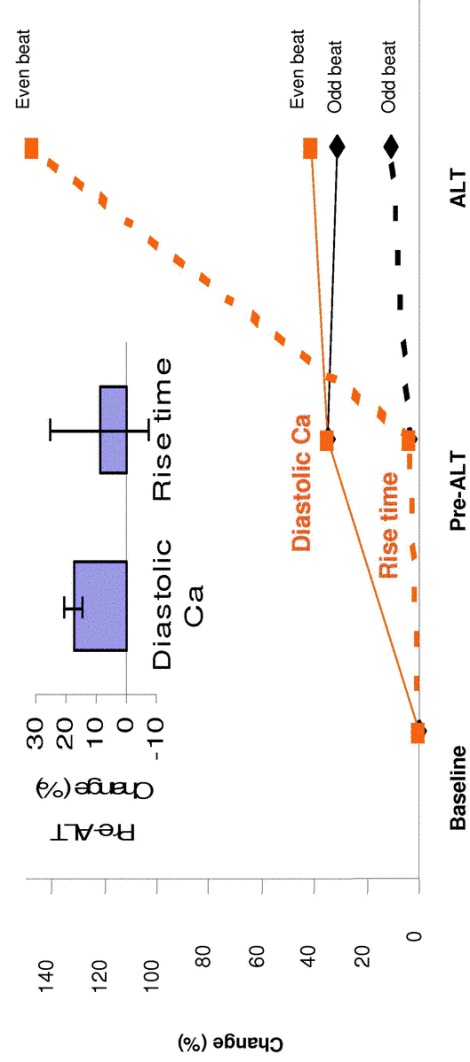
100

60

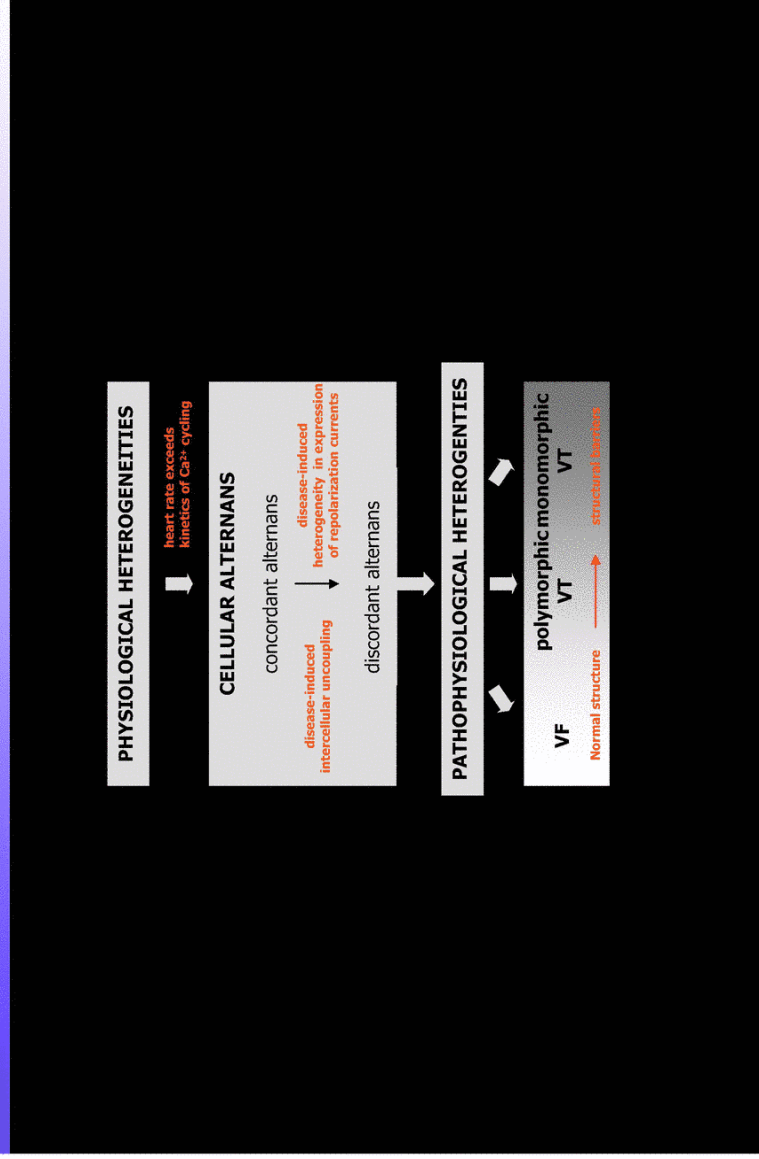
Transmural heterogeneity of calcium handling properties between myocytes



Repolarization alternans is preceded by elevation of cytosolic calcium



# Alternans Hypothesis



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