Pathophysiology and Clinical use of T-Wave Alternans (TWA)

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Noninvasive Approaches

(1) Slowed conduction (QRS duration, signal-averaged electrocardiogram [SAECG])

(2) Heterogeneities in ventricular repolarization (QT interval, QT dispersion, T-wave alternans)

(3) Imbalance in autonomic tone (heart rate variability [HRV], heart rate turbulence, heart rate recovery after exercise, baroreceptor sensitivity),

(4) Extent of myocardial damage and scar formation (left ventricular ejection fraction [LVEF], 6-minute walk)

(5) Ventricular ectopy (longterm ambulatory monitoring)

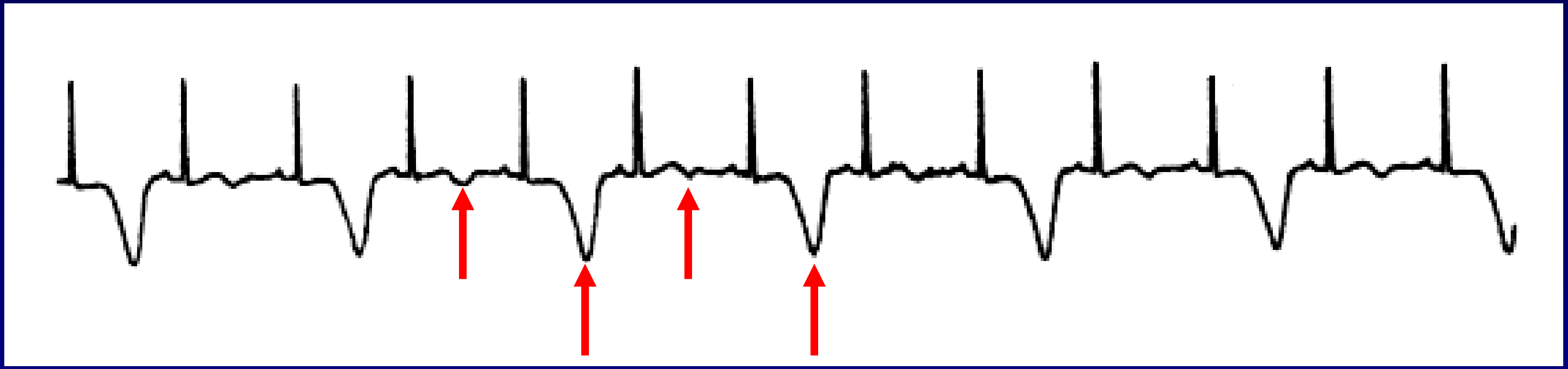
Background

- The only established risk marker for sudden cardiac death (SCD) and the only parameter approved to identify high-risk patients for ICD implantation:

“Depressed LVEF”

Circulation 2010;122:1265–71

T wave Alternans (TWA)

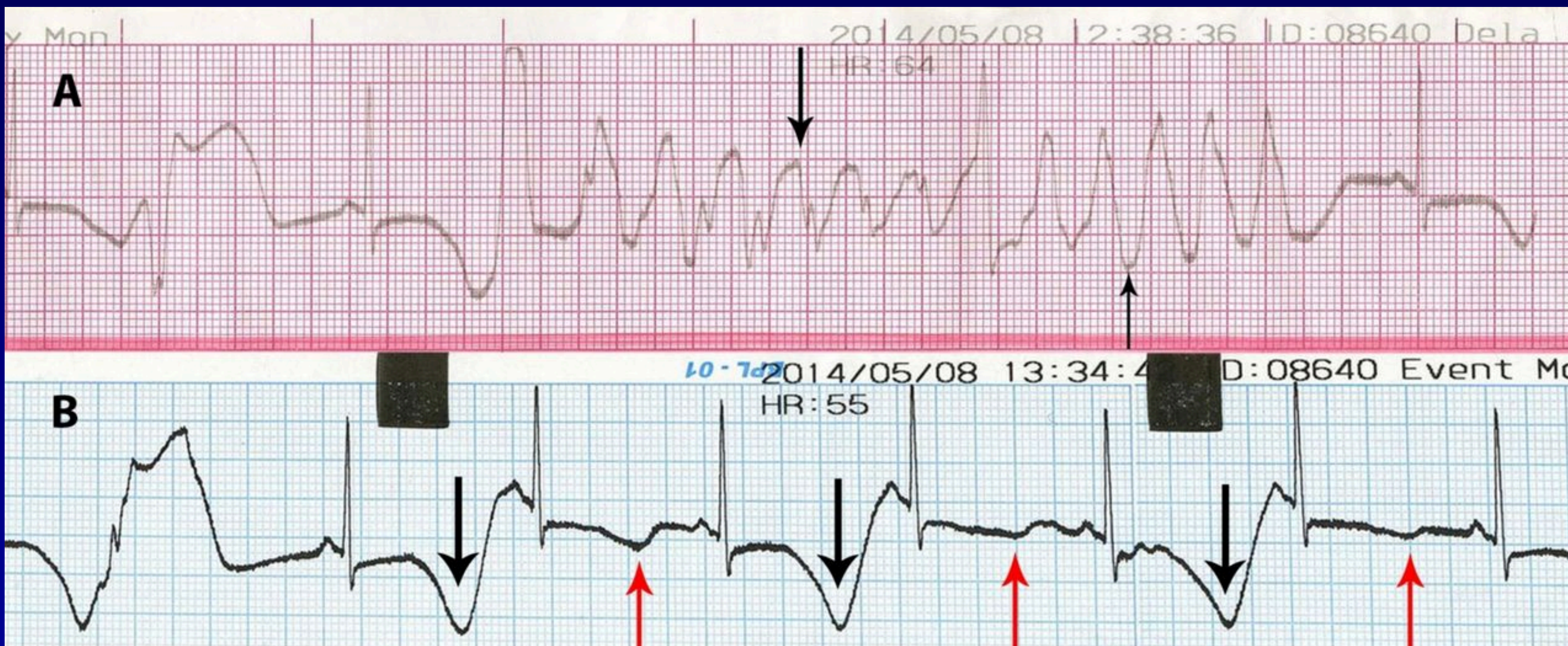


- 1st Electrocardiographic alternans in 1908 by Hering

- A harbinger of malignant ventricular arrhythmia

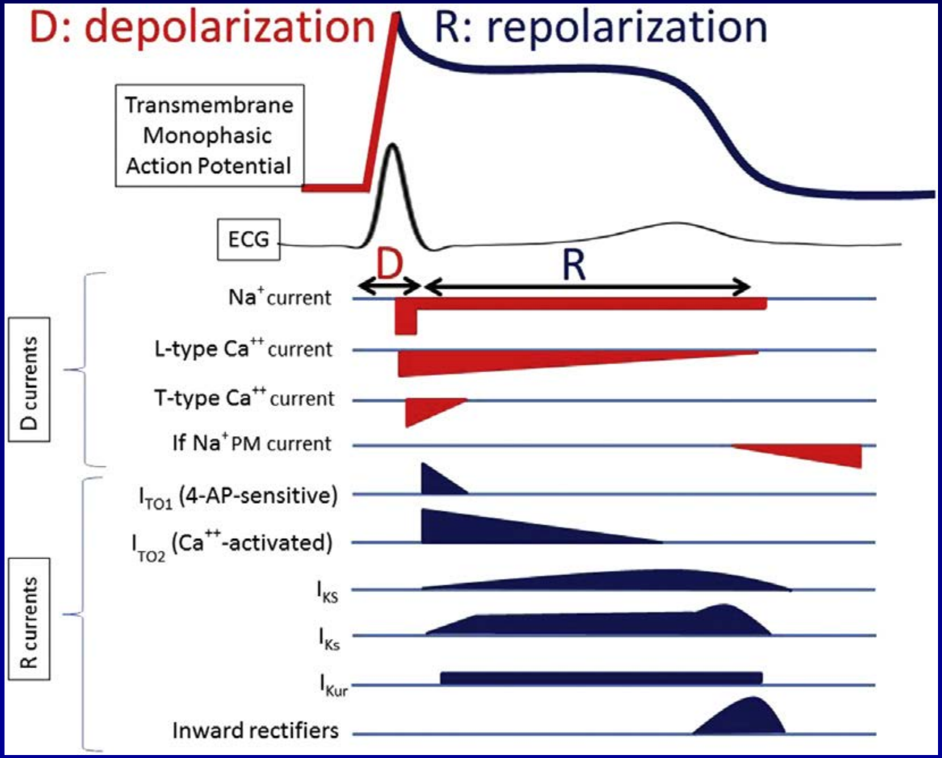
NEJM 1992;326:271-272

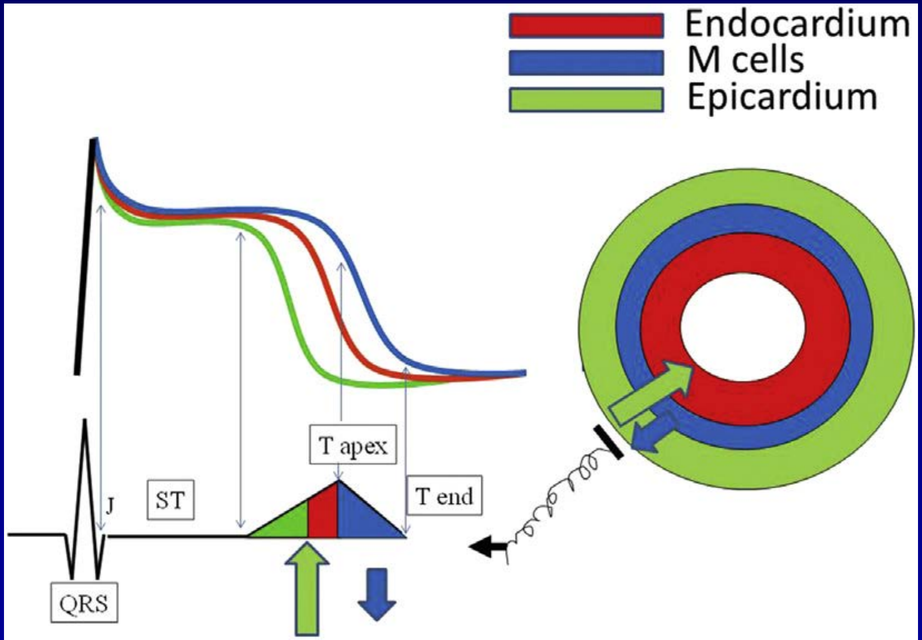
TWA



BMJ Case Reports 2018; doi:10.1136/bcr-2018-225515

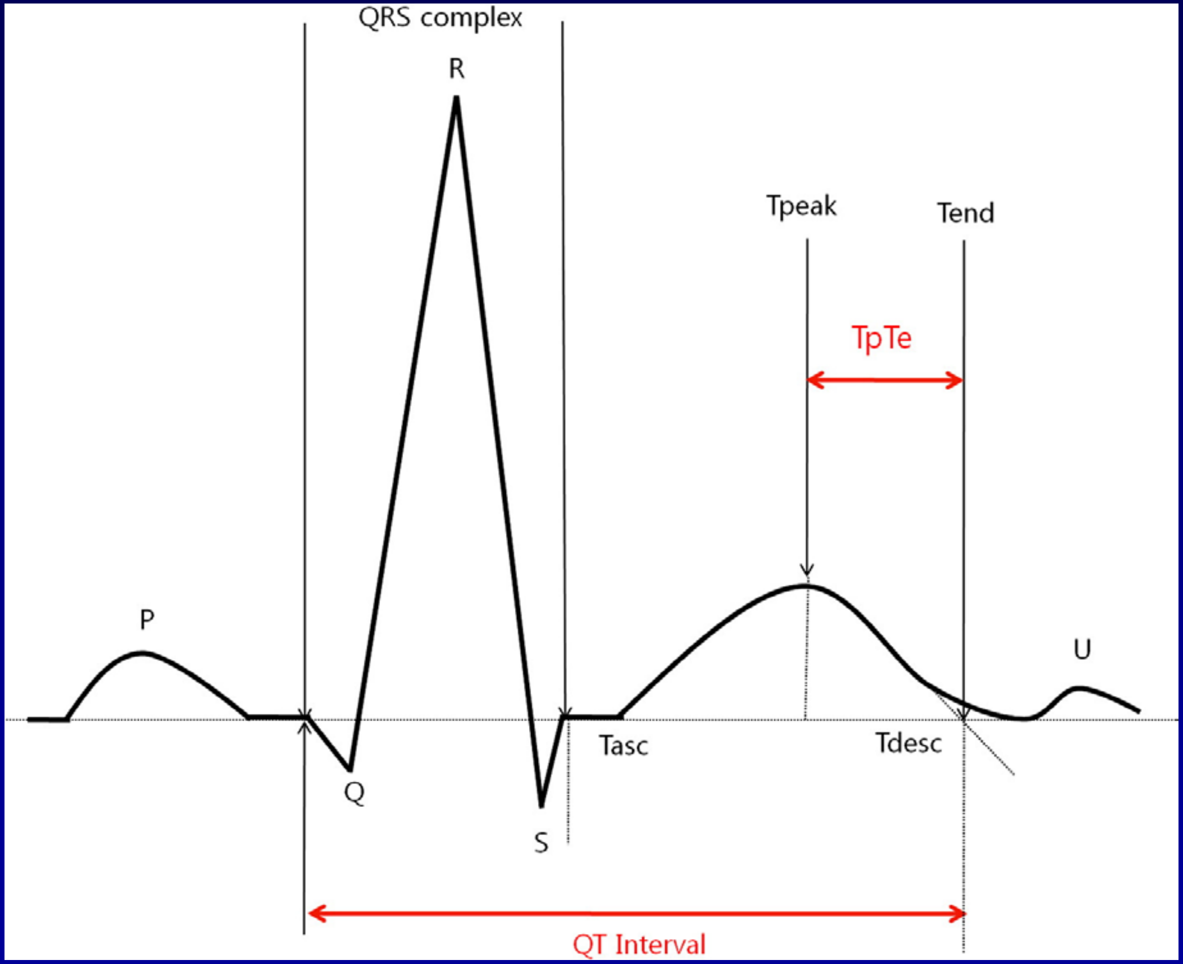
Ventricular Repolarization





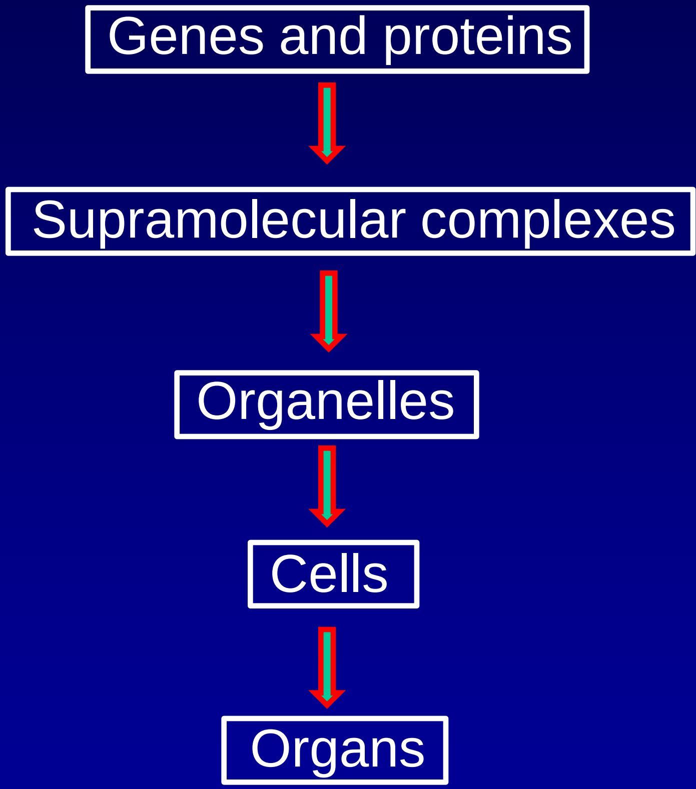
Card Electrophysiol Clin 9 (2017) 487–513

Ventricular Repolarization



Journal of Electrocardiology 47 (2014) 84–92

Fundamental Biological System

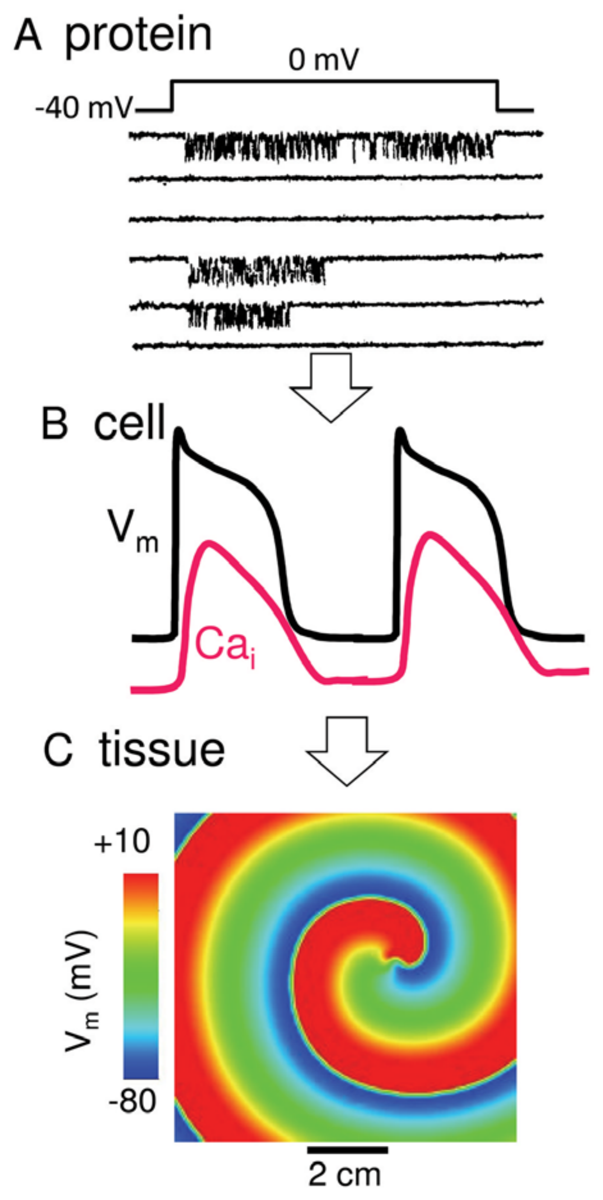


*** Nonlinear interactions**

$$
\begin{aligned}
\partial_t f_i(t,u) &= J_i[\mathbf{f}](t,u) = \sum_{j=1}^{n} J_{ij}[f_i,f_j](t,u) \\
&= \sum_{j=1}^{n} \int_{D_u \times D_u} \eta_{ij}(u_*,u^*)\mathscr{B}_{ij}(u_* \to u \,|\, u_*,u^*) f_i(t,u_*) f_j(t,u^*)\, \mathrm{d}u_*\, \mathrm{d}u^* \\
&\quad - f_i(t,u) \sum_{j=1}^{n} \int_{D_u} \eta_{ij}(u,u^*) f_j(t,u^*)\, \mathrm{d}u^*,
\end{aligned}
$$

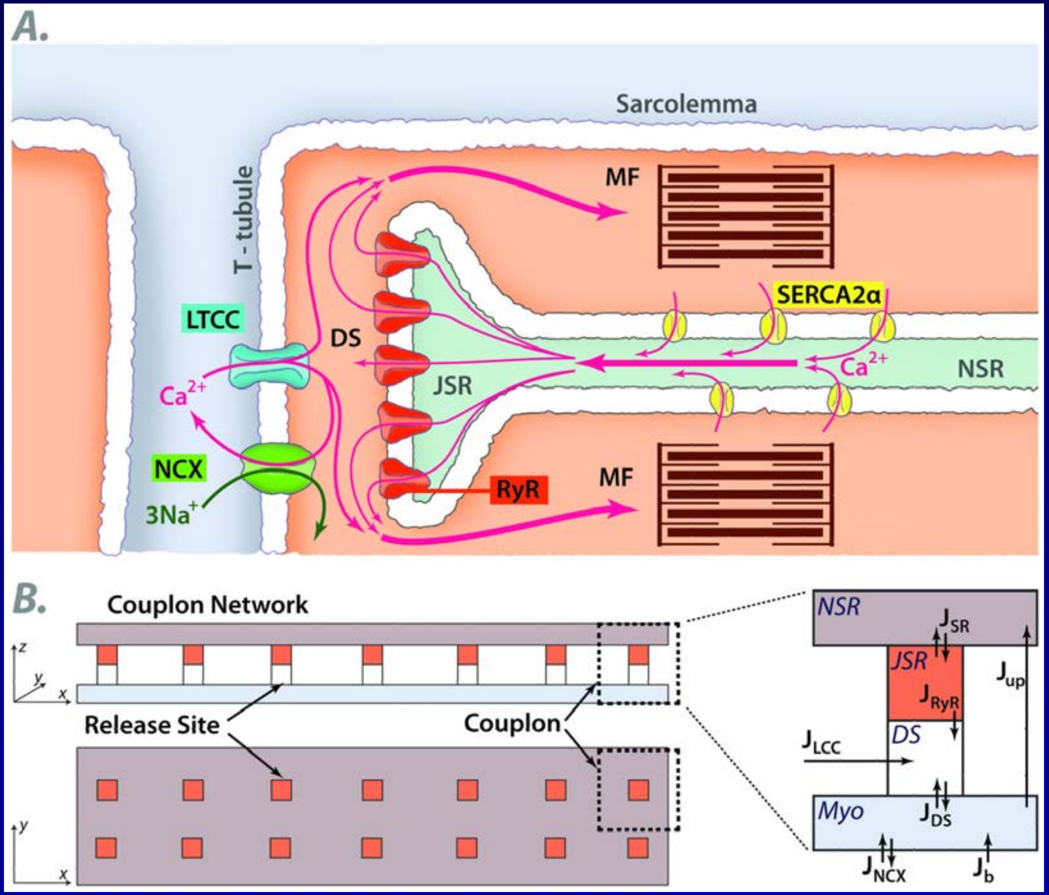
Applied Mathematics Letters 23 (2010) 1372-1377

Fundamental Biological System



Circ Res. 2011 January 7; 108(1): 98–112

Fundamental Ca Release Unit of Cardiac Excitation-Contraction (EC) Coupling
* Couplon



Circ Res. 2011 January 7; 108(1): 98–112

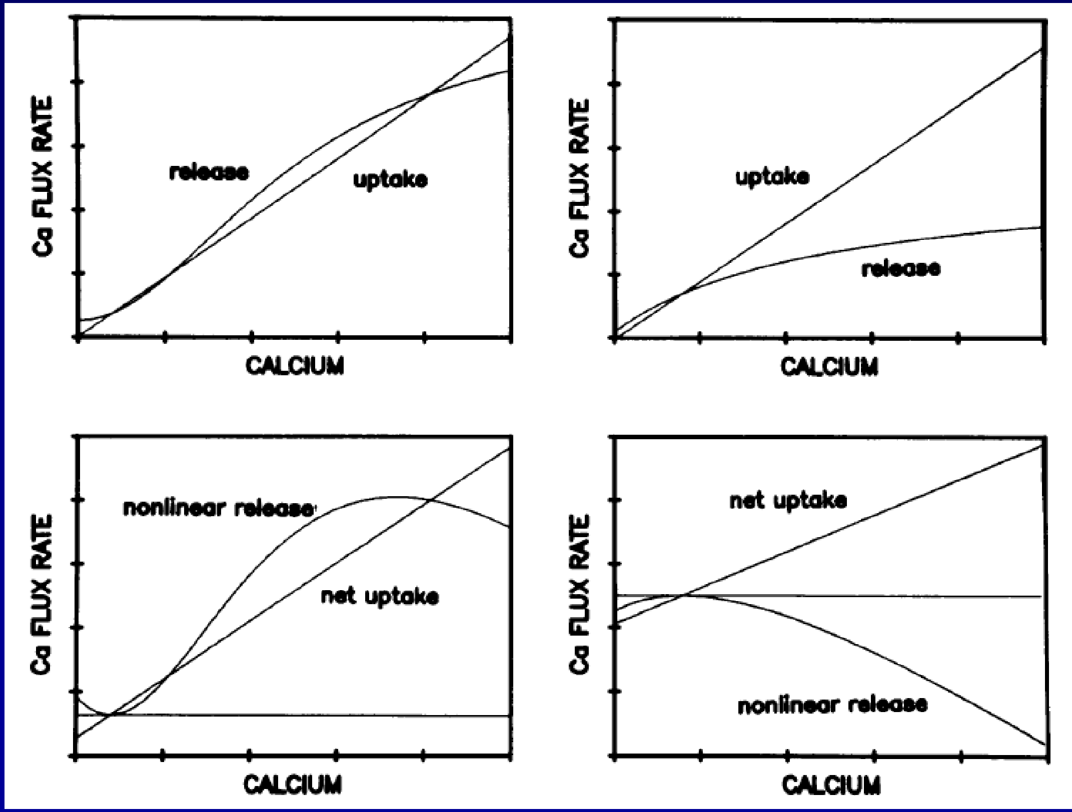
* Couplon: 5–20 LCC and 50–200 RyR

Biophys J. 2005;89(5):3102–3110

Subcellular EC Coupling and the Genesis of Ca Alternans

- Ca-induced Ca release (CICR)

Ca overload → CICR → Ca waves



Biophys J. 1992; 63(2):497–517

Subcellular EC Coupling and the Genesis of Ca Alternans

❖ Ca sparks

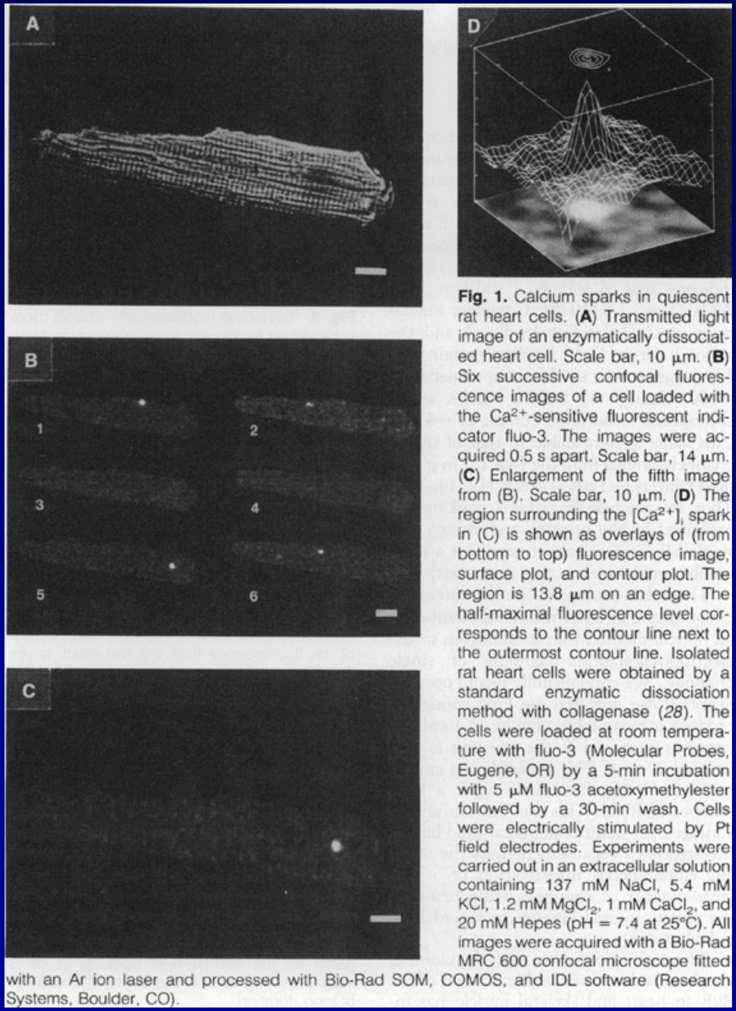


Fig. 1. Calcium sparks in quiescent rat heart cells. (**A**) Transmitted light image of an enzymatically dissociated heart cell. Scale bar, 10 μm. (**B**) Six successive confocal fluorescence images of a cell loaded with the Ca^{2+}-sensitive fluorescent indicator fluo-3. The images were acquired 0.5 s apart. Scale bar, 14 μm. (**C**) Enlargement of the fifth image from (B). Scale bar, 10 μm. (**D**) The region surrounding the $[Ca^{2+}]_i$ spark in (C) is shown as overlays of (from bottom to top) fluorescence image, surface plot, and contour plot. The region is 13.8 μm on an edge. The half-maximal fluorescence level corresponds to the contour line next to the outermost contour line. Isolated rat heart cells were obtained by a standard enzymatic dissociation method with collagenase (*28*). The cells were loaded at room temperature with fluo-3 (Molecular Probes, Eugene, OR) by a 5-min incubation with 5 μM fluo-3 acetoxymethylester followed by a 30-min wash. Cells were electrically stimulated by Pt field electrodes. Experiments were carried out in an extracellular solution containing 137 mM NaCl, 5.4 mM KCl, 1.2 mM $MgCl_2$, 1 mM $CaCl_2$, and 20 mM Hepes (pH = 7.4 at 25°C). All images were acquired with a Bio-Rad MRC 600 confocal microscope fitted with an Ar ion laser and processed with Bio-Rad SOM, COMOS, and IDL software (Research Systems, Boulder, CO).

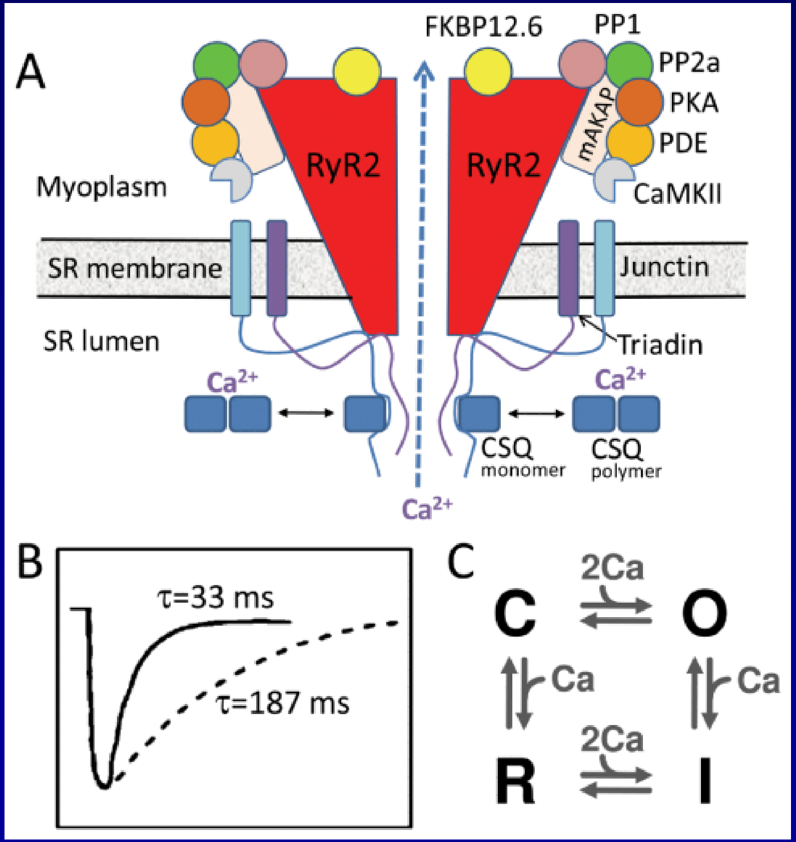
1) Opening of one or more LCC
2) Spontaneous openings of RyR
3) Opening of RyR in response to Ca released from neighboring couplons

Science. 1993; 262(5134):740–744

Subcellular EC Coupling and the Genesis of Ca Alternans

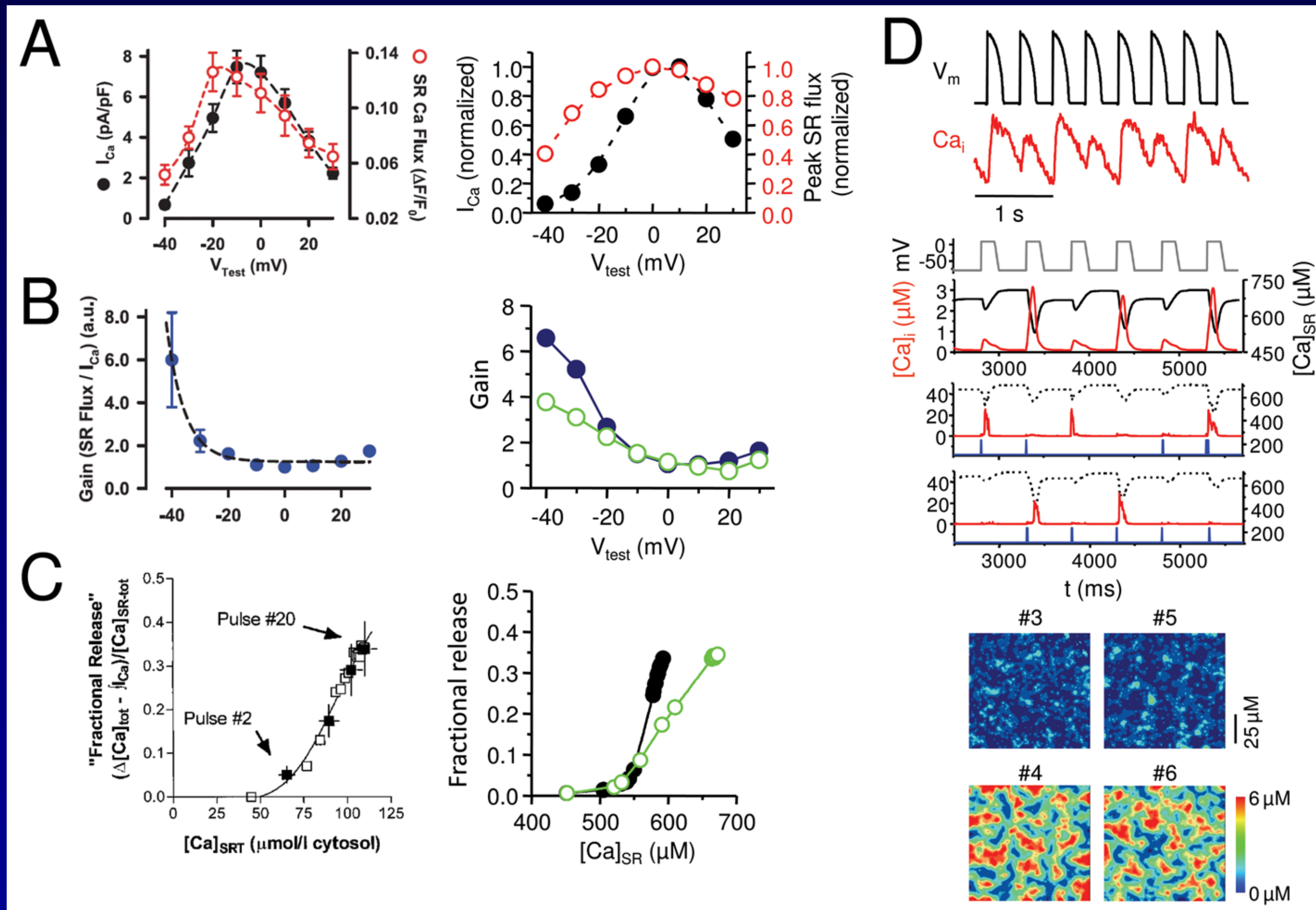
- Three generic properties of the couplon network

  - **- Randomness**
  - **- Refractoriness**
  - **- Recruitment**



Circ Res. 2011 January 7; 108(1): 98–112

Physiological Features of EC Coupling



A. Graded Ca release

B. Voltage dependent EC coupling gain

C. Steep SR fractional release-load relationship

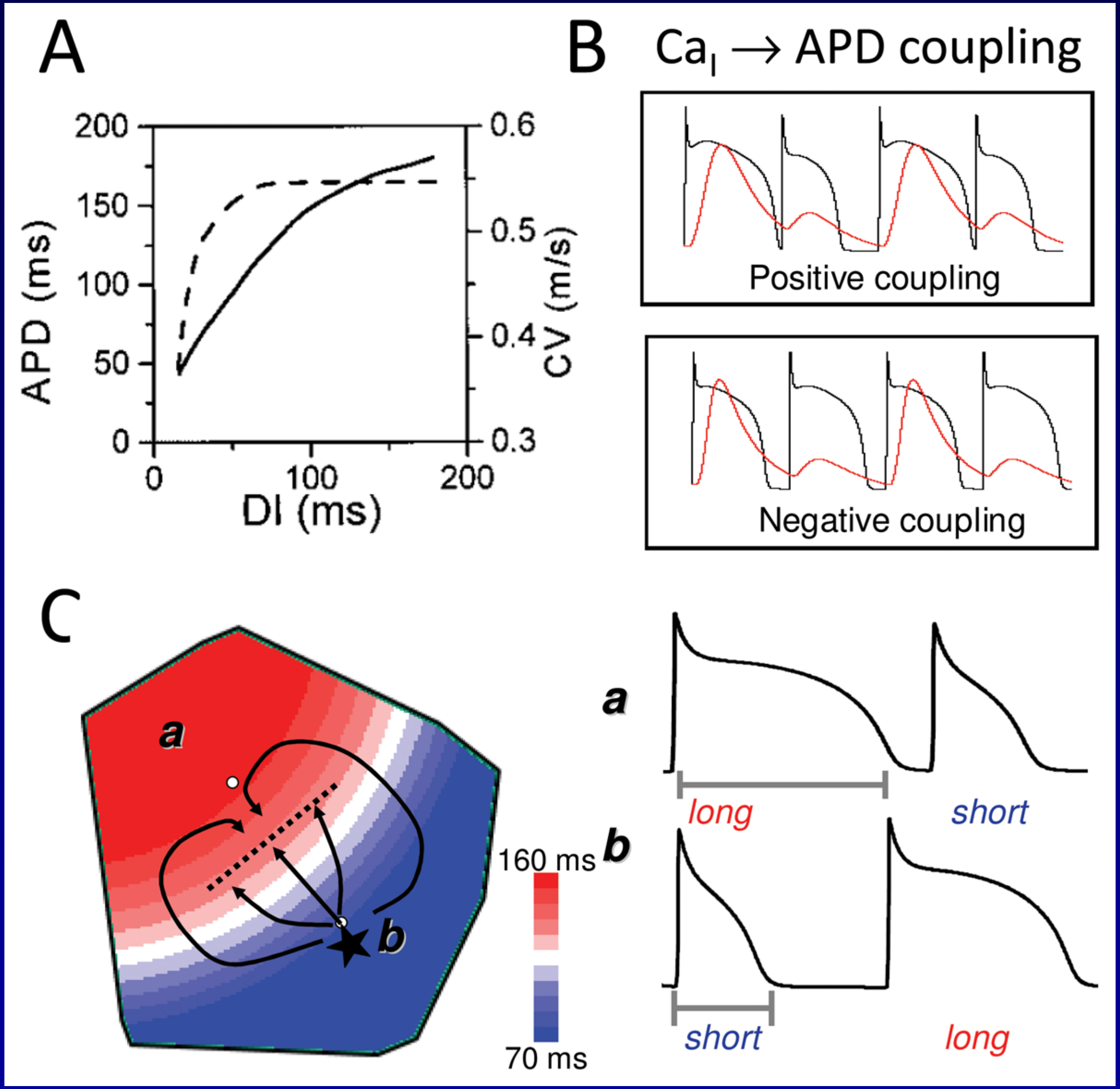
Biophys J. 2000;78(1):334–343

Circ Res. 2007; 101(6):590–597

Pathophysiology of TWA

- **APD restitution**
- **Calcium cycling dynamics**

Positive and Negative Cai-APD Coupling



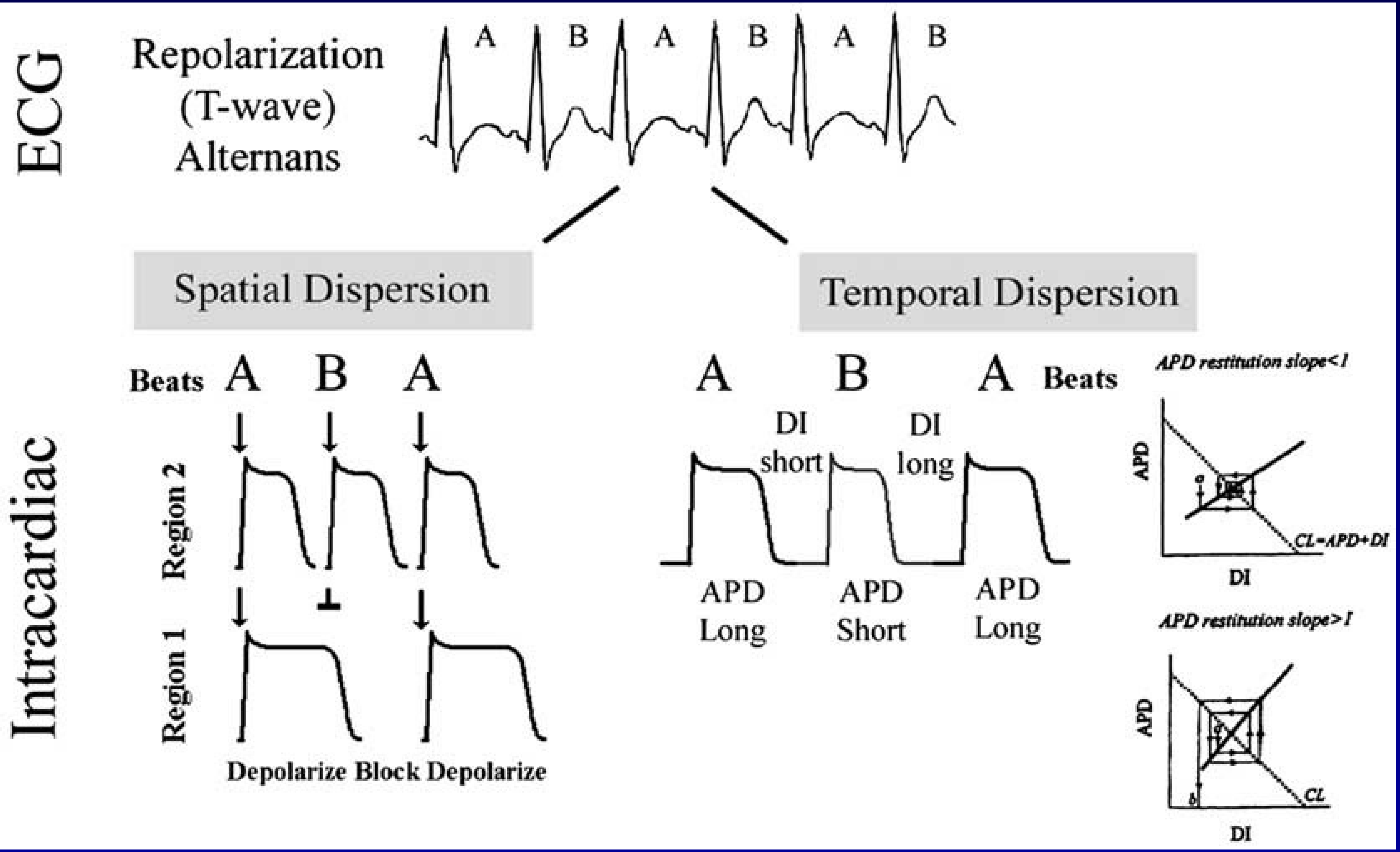
Circ Res. 2011 January 7; 108(1): 98–112

- APD alternans

  = Repolarization alternans

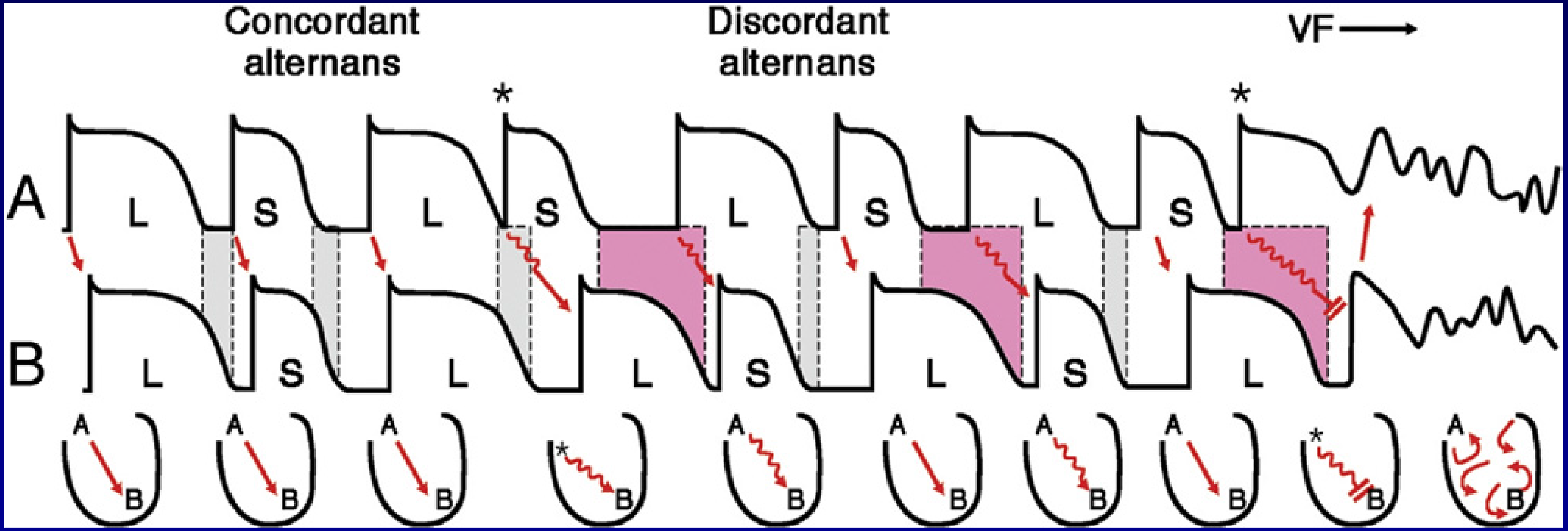
  = T wave alternans

Mechanisms Underlying TWA



Progress in Cardiovascular Diseases, Vol. 51, No. 2 , 2008: pp 118-127

Discordant Alternans Leading to VF



Verrier RL. et al. JACC 2011

Influence of Physiological Interventions on TWA

Amplified by

- increased heart rates (Cardiovasc Res 1994)
- ventricular premature beats (Circulation 1999)
- coronary artery occlusion and reperfusion (Circ Res 2002)
- adrenergic stimulation (Science 1991)
- mental stress (J Am Coll Cardiol 2009)

Calcium Cycling and TWA in Myocardial Ischemia and Heart Failure

"Derangements in calcium cycling and conduction: ionic bases for TWA during myocardial ischemia and heart failure"

- Ischemia induce concordant and discordant alternation in calcium transients

Am J Physiol Heart Circ Physiol 2008

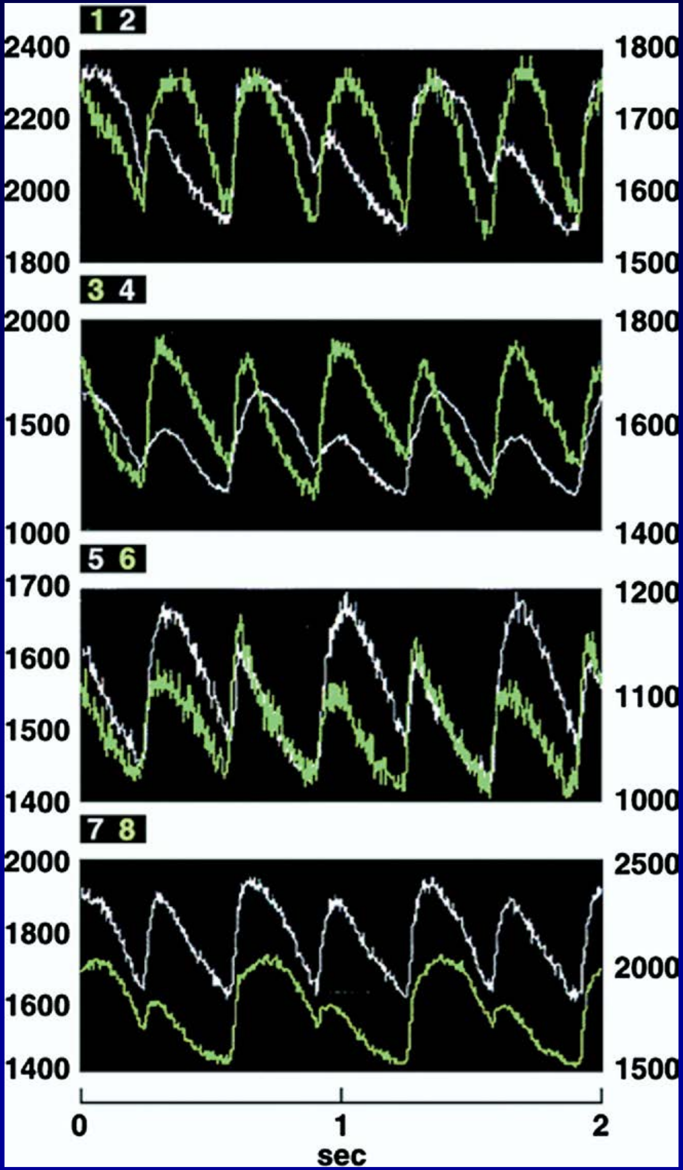
- Heart failure reduced SR Ca^{2+}-adenosine triphosphatase expression and inhibited ryanodine receptor function, resulting in impaired reuptake and release of calcium in the SR

Am J Physiol Heart Circ Physiol 2008
Heart Rhythm 2009

- TWA may be attributable to oscillations in the action potential plateau that, in computational models, were best explained by reduced calcium uptake into the SR in cardiomyopathy patients

J Am Coll Cardiol 2008

Cai Transients During Myocardial Ischemia



Heart Rhythm, Vol 6, No 3, March 2009

Methodology for TWA Assessment

- Micro-level T wave alternans (mTWA)

  - 1st reported in 1982

IEEE Comput Cardiol 1982:241-4

  - Strong relationship between the presence of mTWA and vulnerability to ventricular arrhythmia

NEJM 1994;330:235-41

Methodology for mTWA Assessment

- Spectral Method (Cambridge Heart, Bedford, MA)

- Modified Moving Average (MMA) Methods
  (GE Medical Systems, Milwaukee, WI)

Spectral TWA Method

Spectral Method

1) Exercise protocol

Increase heart rate to 105-110 beats/min by bicycle ergometer

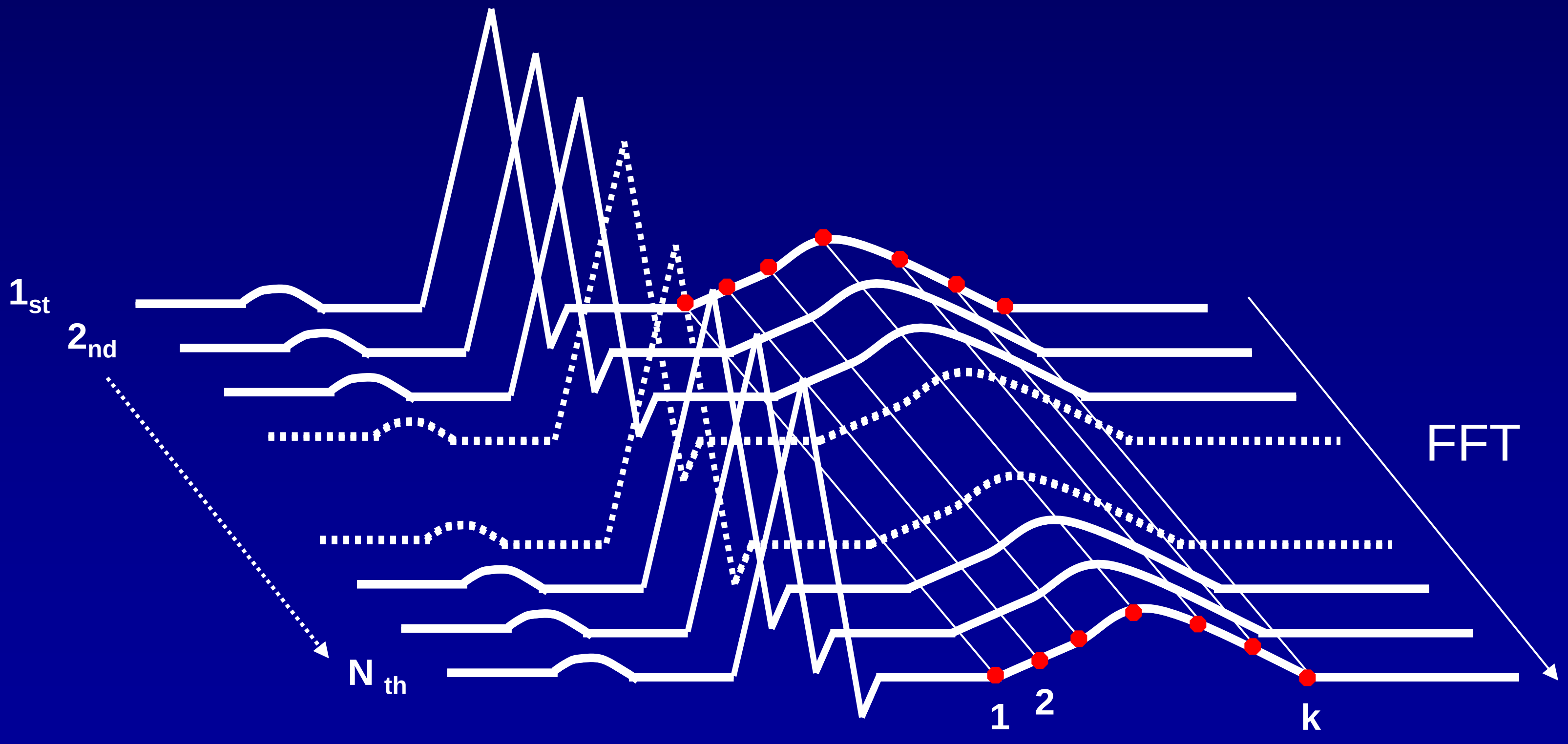
2) Fast Fourier transformation (FFT)

Beat-to-beat fluctuations in the amplitudes of T waves from 128 consecutive beats

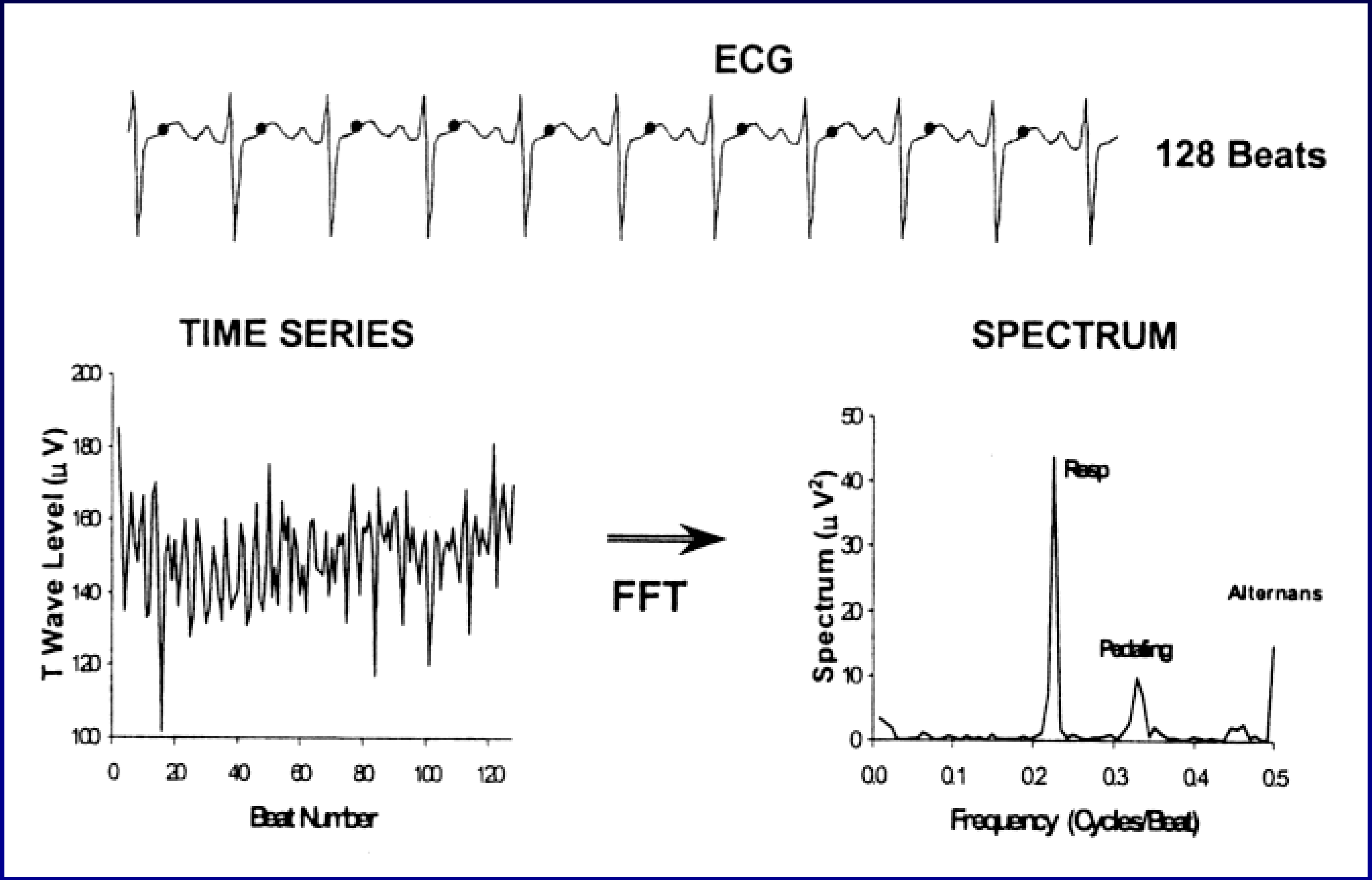
→ Power spectra

Spectral TWA Method

Arrangement of QRS and ST-T segment according to continuous sequence



Spectral TWA Method



J Cardiovasc Electrophysiol 2002;13:502-512

* Alternans ratio (R_{alt}) = alternans power ($\sum T-\mu_{noise}$)/σ_{noise}

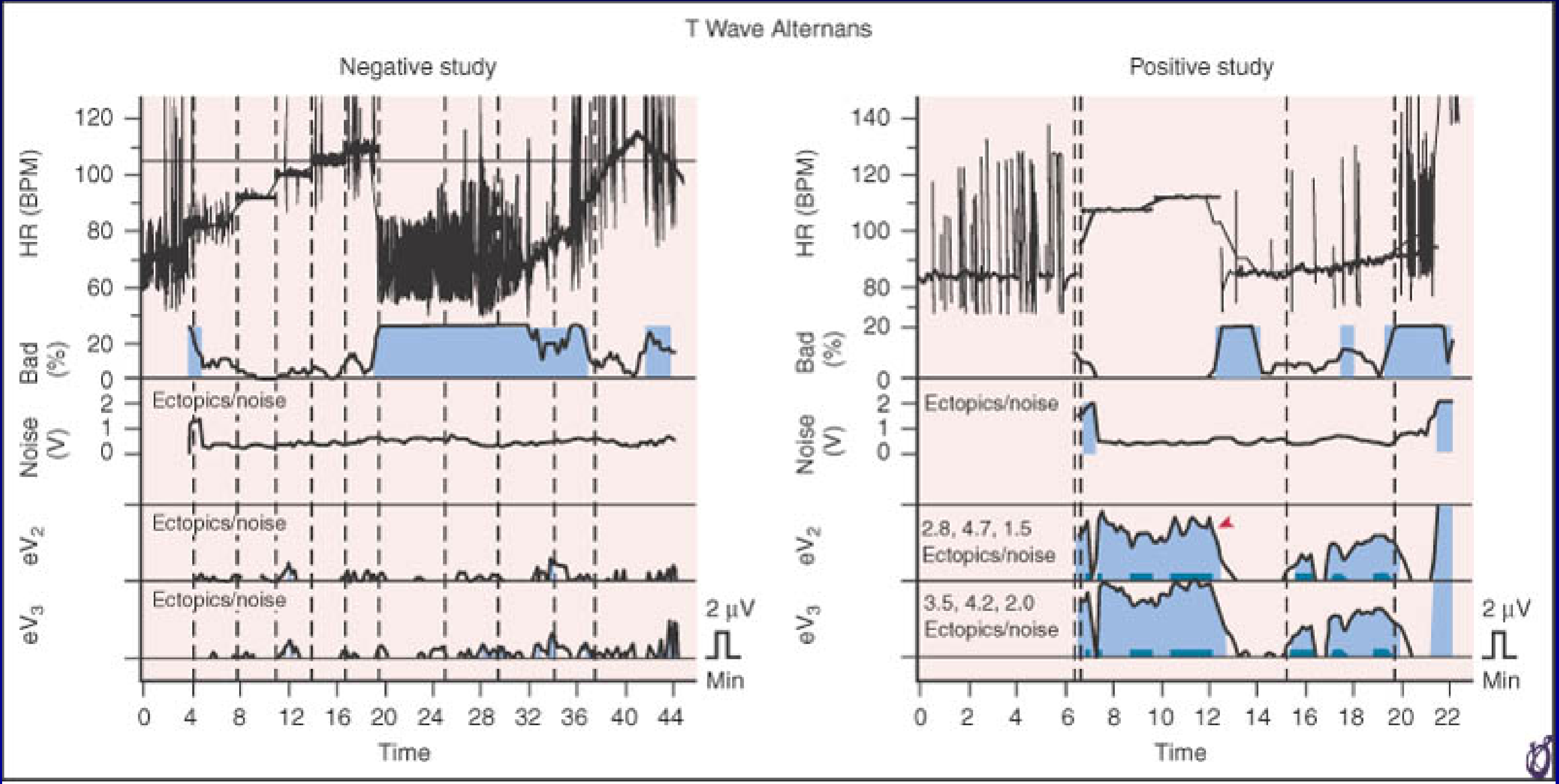
* Alternans voltage (V_{alt}) = $\sqrt{\sum T-\mu_{noise}}$/ST-T duration

Spectral TWA Method

3) Definitions

- Positive: - $V_{alt} \geq 1.9\ \mu V$
  - $R_{alt} \geq 3.0$
  - Duration >2 min with HR ≤110 BPM
- Negative: - Test results below this level
- Indeterminate

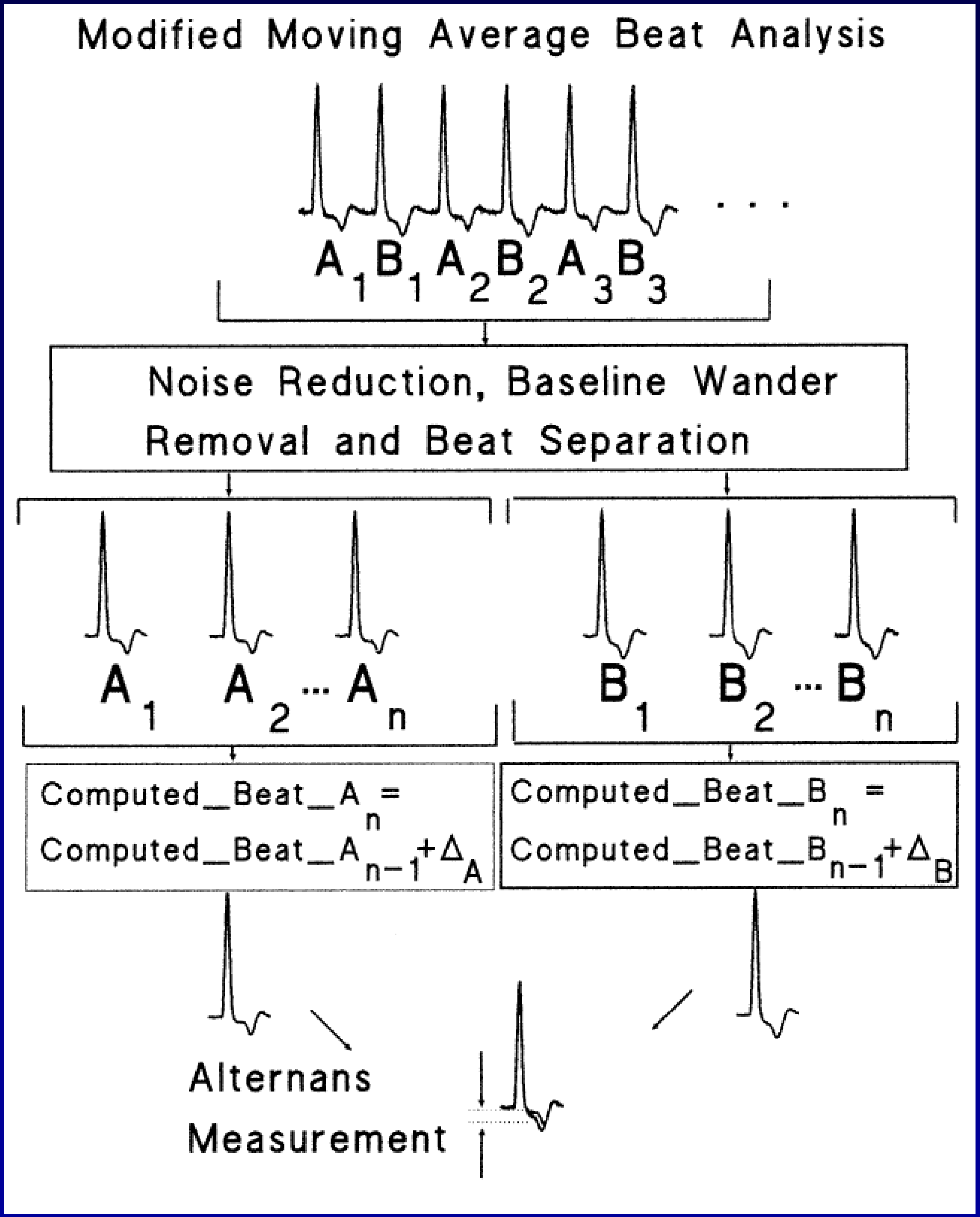
mTWA



Braunwald's Heart Disease 8th edition

MMA TWA Method

MMA TWA Method



During
- routine, symptom-limited exercise stress testing

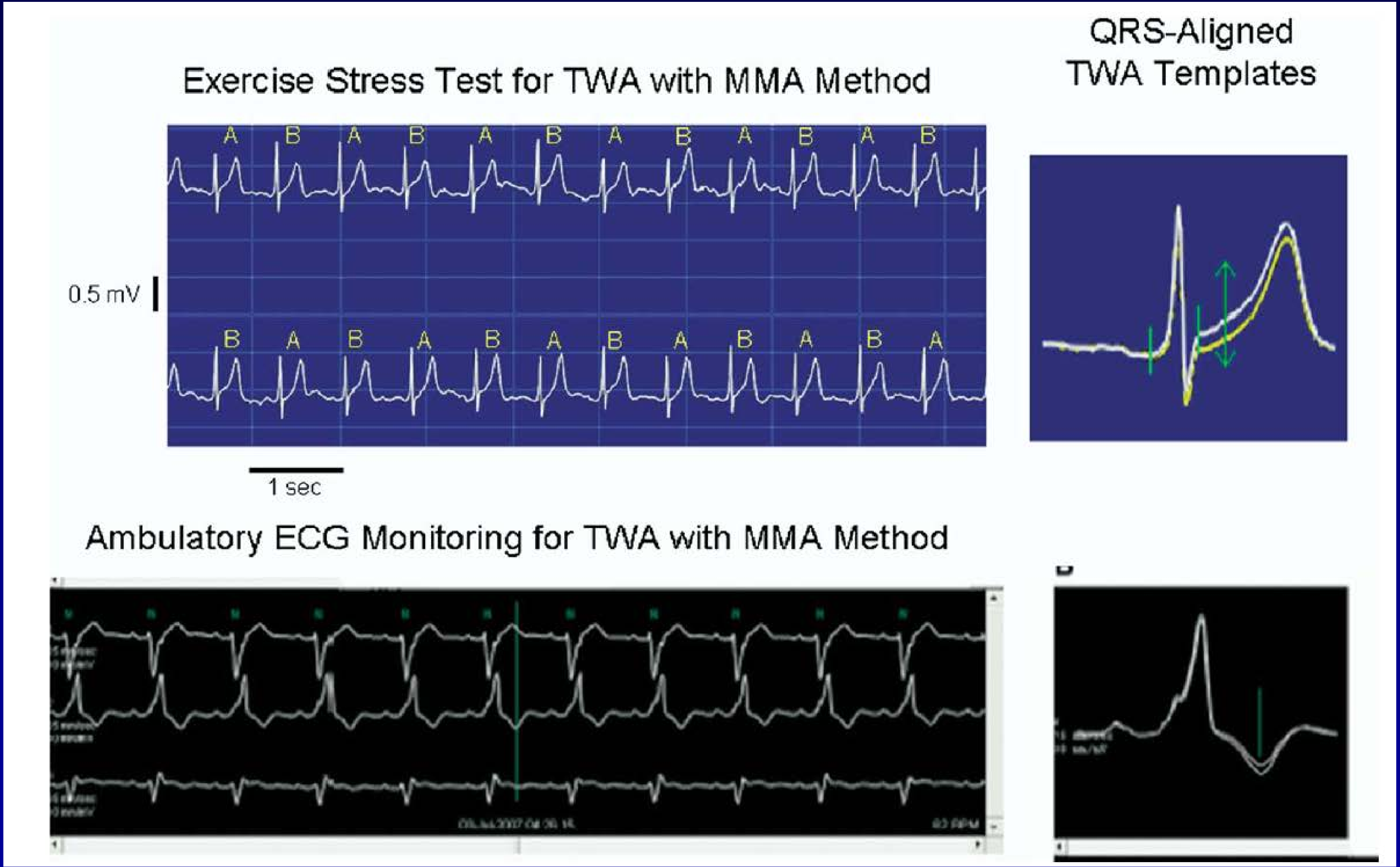
- post-exercise recovery

- ambulatory ECG monitoring

"Calculated from standard precordial ECG leads with standard electrodes"

J Cardiovasc Electrophysiol 14:70S, 2003

MMA TWA Method



Heart Rhythm 2009;6:416–422

Clinical use of TWA

Spectral TWA Method

Clinical Utility

- Significant predictivity of TWA analysis by the Spectral Method
  : Prospectively demonstrated in >7,200 patients with various types of cardiovascular disease, including myocardial infarction, CHF, ischemic CMP, and nonischemic DCMP

J Am Coll Cardiol 2007;50:1896 –904
J Am Coll Cardiol 2007;50:2275– 84

- Event-free survival from all-cause or cardiac mortality and/or ventricular tachyarrhythmias averaged 97% to 98% in patients with negative TWA test results

MADIT II. Circulation 2004;110:1885–9
Lancet 2003;362:125– 6

- TWA stratified total mortality did not predict sudden cardiac death or appropriate ICD discharge in the MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial of MADIT II-type patients and the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) TWA substudy

J Am Coll Cardiol 2008;52:1607–15
Circulation 2008;118:2022– 8

MMA TWA Method

- TWA ≥ 60 µV during routine exercise testing and ambulatory ECG monitoring
  : severely elevated risk for sudden cardiac death

J Am Coll Cardiol 2009;53:1130 –7

- During the early post-MI phase with or without heart failure, a cutpoint of 47 µV also predicted sudden cardiac death

J Cardiovasc Electrophysiol 2008;19:1037– 42

- A 55% and 58% increase in risk of cardiovascular and sudden cardiac death, respectively, per 20 µV of TWA

Heart Rhythm 2011;8:385–90

MMA TWA Method

Clinical Utility

- Predictivity of TWA analysis by the MMA method
  : demonstrated in > 4,800 patients, including those with coronary artery disease, recent or old MI, CHF, or cardiomyopathy

Eur Heart J 2007;28:2332–7
J Cardiovasc Electrophysiol 2009;20:408 –15
Heart Rhythm 2011;8:385–90
Heart Rhythm 2009;6:1765–71

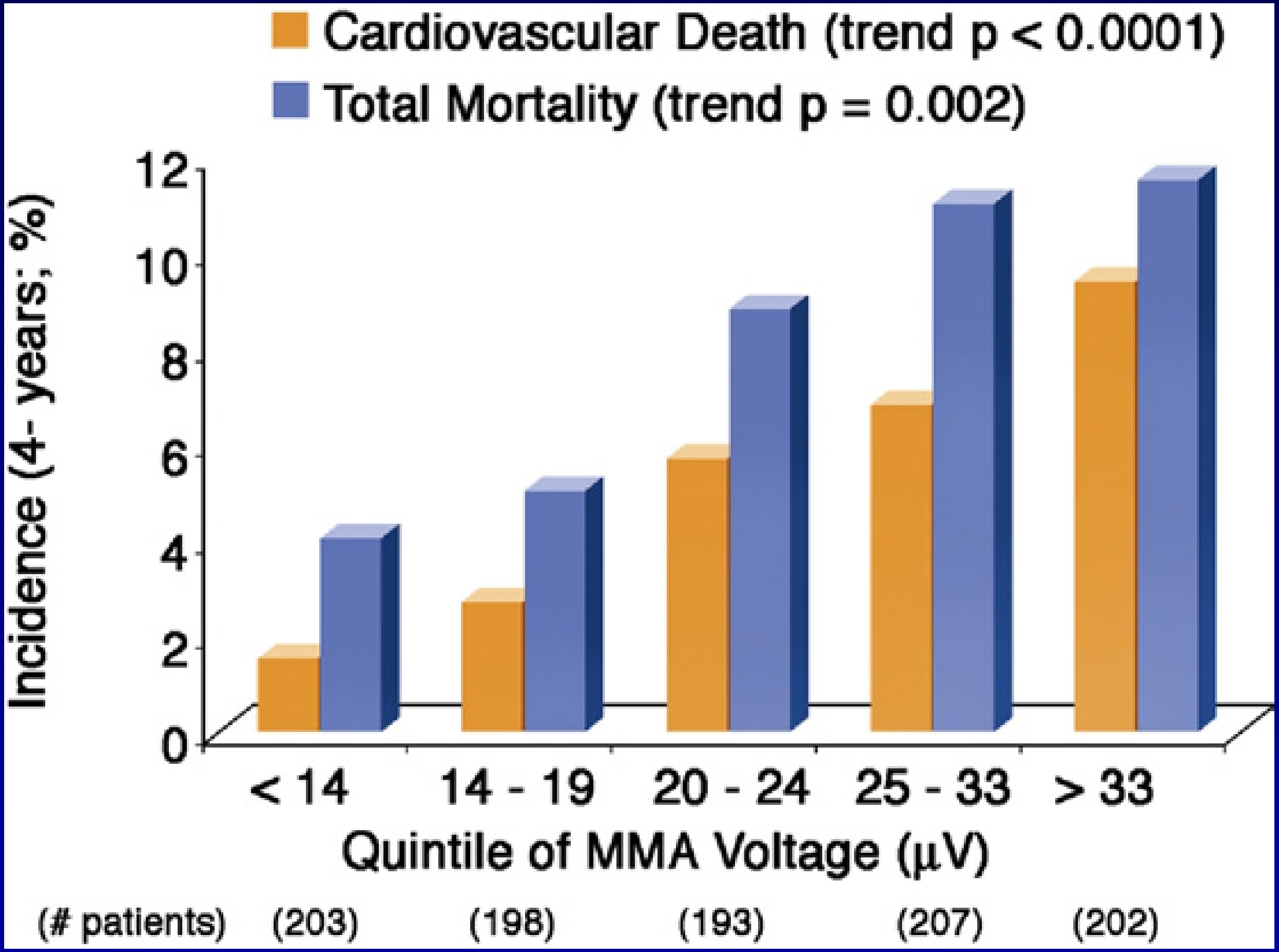
- MMA-based TWA is predictive
  - immediate post-exercise recovery

J Am Coll Cardiol 2007;50:2275– 84
J Am Coll Cardiol 2009;53:1130 –7
Heart Rhythm 2009;6:1765–71

  - From ambulatory ECG records

J Cardiovasc Electrophysiol 2003;14:705–11
J Cardiovasc Electrophysiol 2008;19:1037– 42
Heart Rhythm 2009;6:332–7
Circ J 2009;73:2223– 8
J Electrocardiol 2010;43:251–9

Quantitative Analysis of TWA Voltage MMA method



J Am Coll Cardiol 2009;53:1130 –7

Comparison of the Predictivity of TWA With the Spectral and MMA Methods

- Spectral Method: one-half of the average TWA magnitude across the entire JT interval for 128 beats
- MMA method: the peak TWA level at any point within the JT interval for each 10 to 15-s interval

• Hazard ratios for prediction by the Spectral and MMA methods are similar, whether in the same population or in studies overall

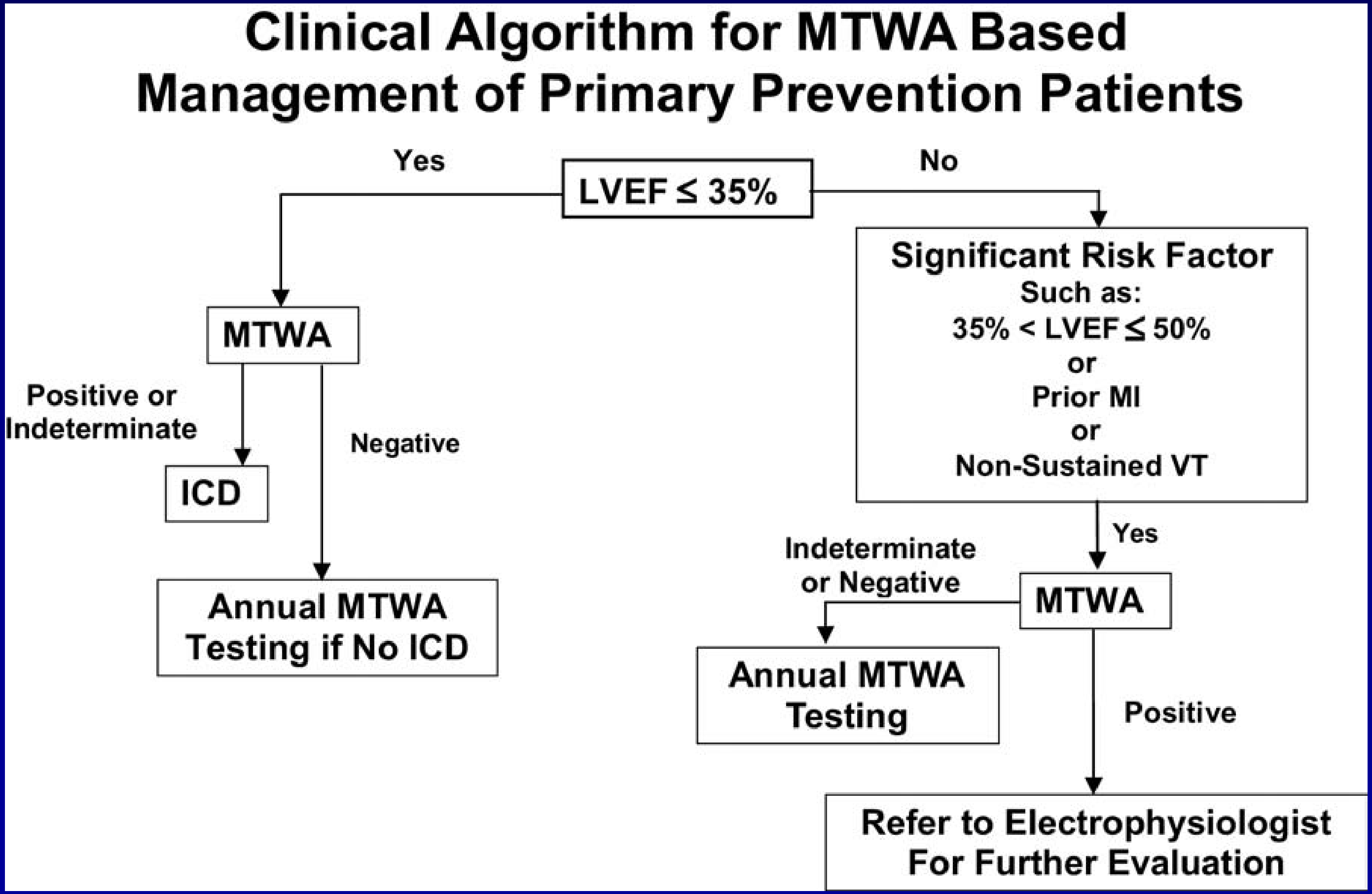
• TWA assessed by the Spectral Method during exercise and by the MMA method during the post-exercise recovery phase yielded significant odds ratios of 2.75 and 2.94, respectively, in 322 postmyocardial infarction patients with better-preserved LVEF

J Am Coll Cardiol 2007;50:2275– 84

Clinical Algorithm and TWA

- Event-free survival from all-cause or cardiac mortality and/or ventricular tachyarrhythmias averaged 97% to 98% in patients with negative micro T wave alternans (mTWA) test results

Lancet 2003;362:125– 6



Stefan H. Hohnloser, MD, Takanori Ikeda, MD, Richard J. Cohen, MD, PhD. Heart Rhythm 2009;6:S36–44

2015 ESC Guidelines

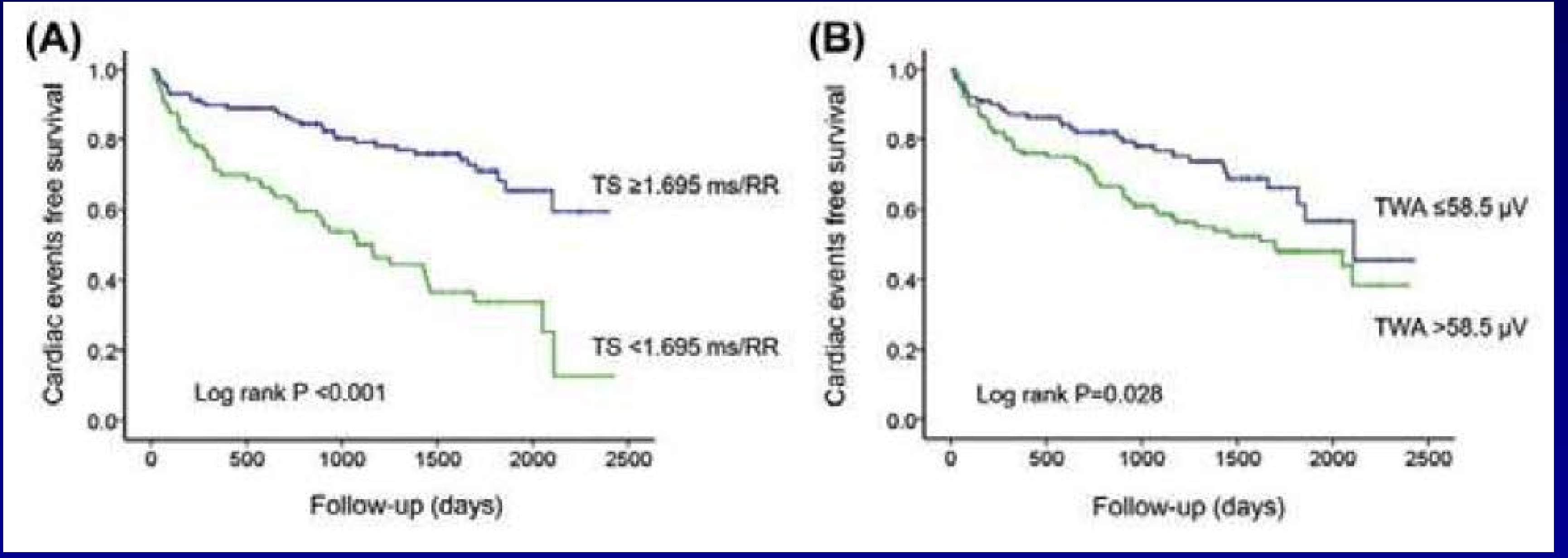
Non-invasive evaluation of patients with suspected or known ventricular arrhythmias

Non-invasive evaluation of patients with suspected or known ventricular arrhythmias

Recommendations	Class[a]	Level[b]	Ref.[c]
Resting 12-lead ECG			
Resting 12-lead ECG is recommended in all patients who are evaluated for VA.	I	A	1
ECG monitoring			
Ambulatory ECG is recommended to detect and diagnose arrhythmias. Twelve-lead ambulatory ECG is recommended to evaluate QT-interval changes or ST changes.	I	A	93
Cardiac event recorders are recommended when symptoms are sporadic to establish whether they are caused by transient arrhythmias.	I	B	94
Implantable loop recorders are recommended when symptoms, e.g. syncope, are sporadic and suspected to be related to arrhythmias and when a symptom–rhythm correlation cannot be established by conventional diagnostic techniques.	I	B	95
SA-ECG is recommended to improve the diagnosis of ARVC in patients with VAs or in those who are at risk of developing life-threatening VAs.	I	B	96,97
Exercise stress testing			
Exercise stress testing is recommended in adult patients with VA who have an intermediate or greater probability of having CAD by age and symptoms to provoke ischaemic changes or VA.	I	B	98
Exercise stress testing is recommended in patients with known or suspected exercise-induced VA, including CPVT, to achieve a diagnosis and define prognosis.	I	B	99
Exercise stress testing should be considered in evaluating response to medical or ablation therapy in patients with known exercise-induced VA.	IIa	C	1
Imaging			
Echocardiography for assessment of LV function and detection of structural heart disease is recommended in all patients with suspected or known VA.	I	B	100, 101

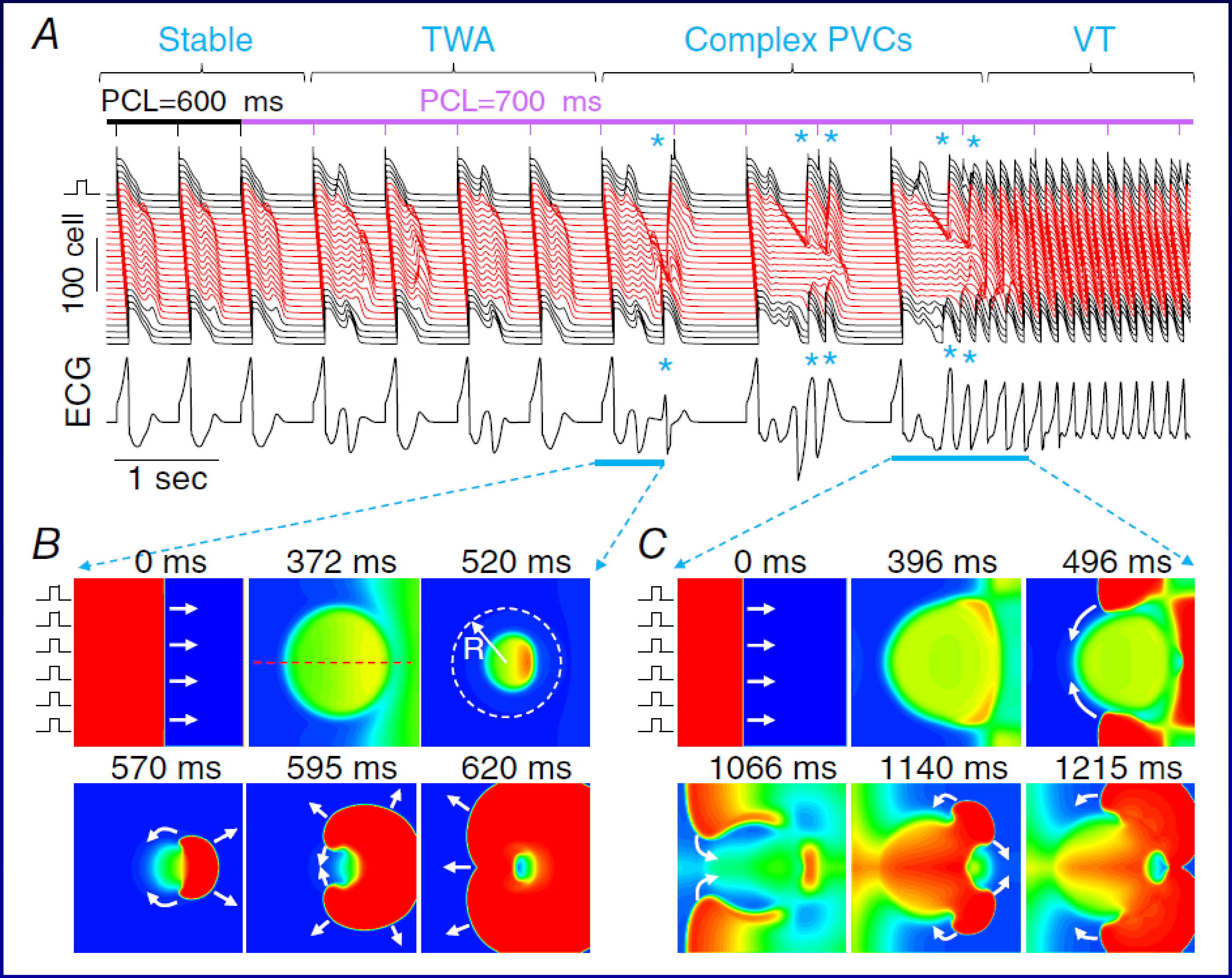
* No recommendations for the use of TWA in risk assessment

Cardiac Events in Heart Failure Patients



J Cardiovasc Electrophysiol. 2018;29:1257–1264

Arrhythmias Induced Following TWA in a LQT2 Rabbits Model



J Physiol 596.8 (2018) pp 1341–1355

Ongoing Trials

- REFINE-ICD trial
- K-REDEFINE

Conclusions

- Alterations in intracellular calcium cycling are an important basis for repolarization alternans
- Dynamic instabilities in the form of TWA can also result from changes in membrane voltage due to steep APD restitution
- TWA has remained a promising tool to assess the vulnerability to lethal arrhythmias among patients with cardiac disease, but there is not enough clinical evidence to support the use of TWA testing in routine clinical practice to guide therapy