Cardiovascular Effects of Space Flight

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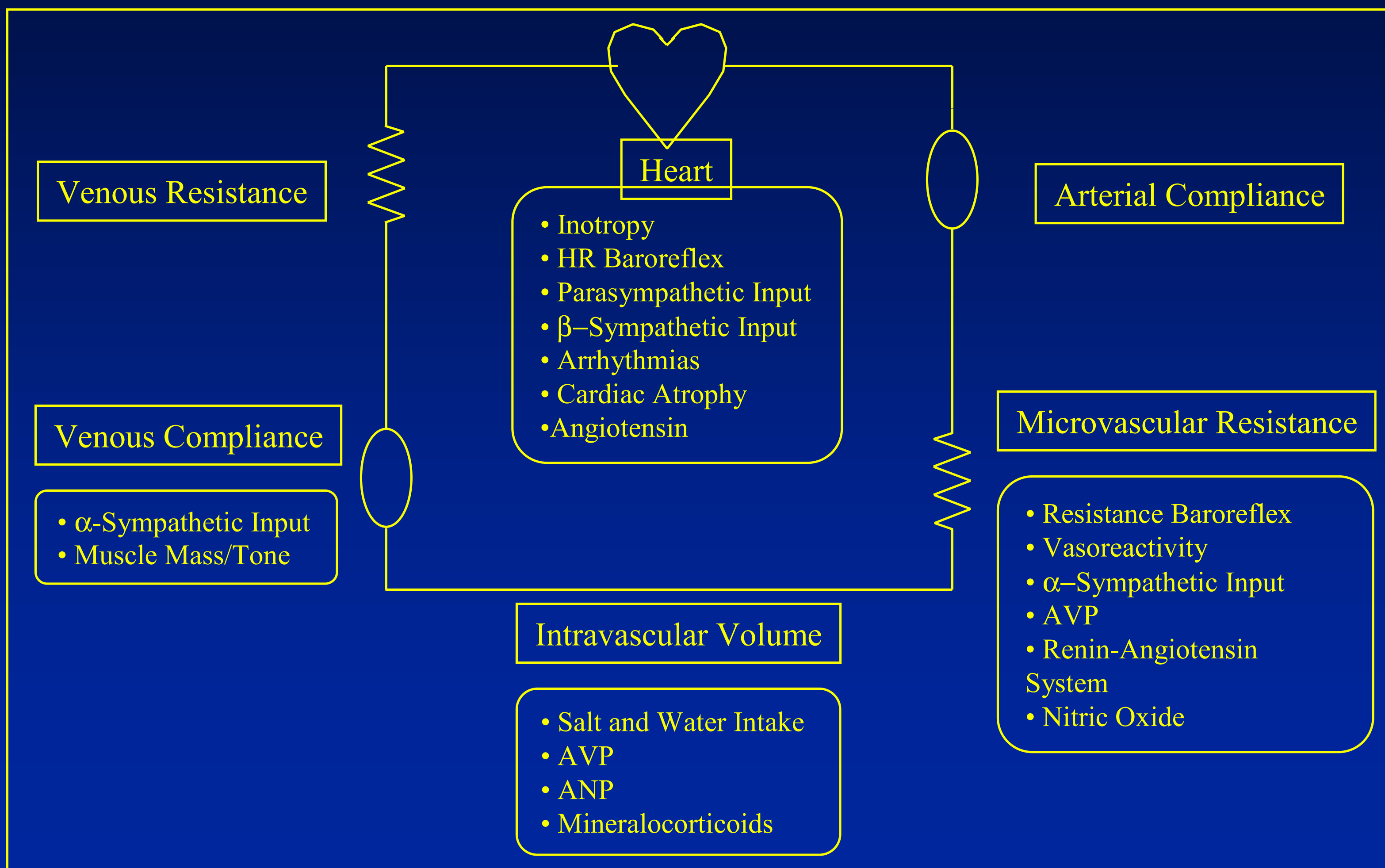
Cardiovascular Problems Associated with Space Flight

- Orthostatic Intolerance upon Re-entry
- Arrhythmias
- Loss of Cardiac Mass
- Reduced Exercise Capacity
- Manifestation of Pre-existing Cardiovascular Disease

Post Flight Orthostatic Intolerance

- Appears to be more severe the longer the duration of space flight.
- Women are more severely affected than men, but virtually all are affected after long duration flight.
- Current countermeasures of salt and water loading and use of a G suit are not adequate

Cardiovascular Problems Associated with Space Flight



Cardiovascular Problems

Deconditioning

Atrophy

Arrhythmias

Human Studies

Human Studies Core - Williams

Alteration in Cardiovascular Regulation - Cohen

Renal and Cardio-Endocrine Responses - Williams

Ventricular Arrhythmias - Cohen

Rodent Studies

Cardiovascular Deconditioning - Shoukas

Cardiac Atrophy - Schneider

Computer Modeling

Kamm

Actions

Determine Magnitude of Problem

Identify Mechanisms

Propose Countermeasures

Test Countermeasures

Effects of Microgravity on Cardiovascular, Hormonal and Renal Response to Posture

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Gordon Williams, M.D.

Disciplines: Cardiology, Endocrinology, Space Medicine

Primary Source of Funding: National Space Biomedical Research Institute

Experiment Protocol

2 Days
Extensive
CV & Endocrine
Testing

→

16 Days
4º HDT
Bed rest

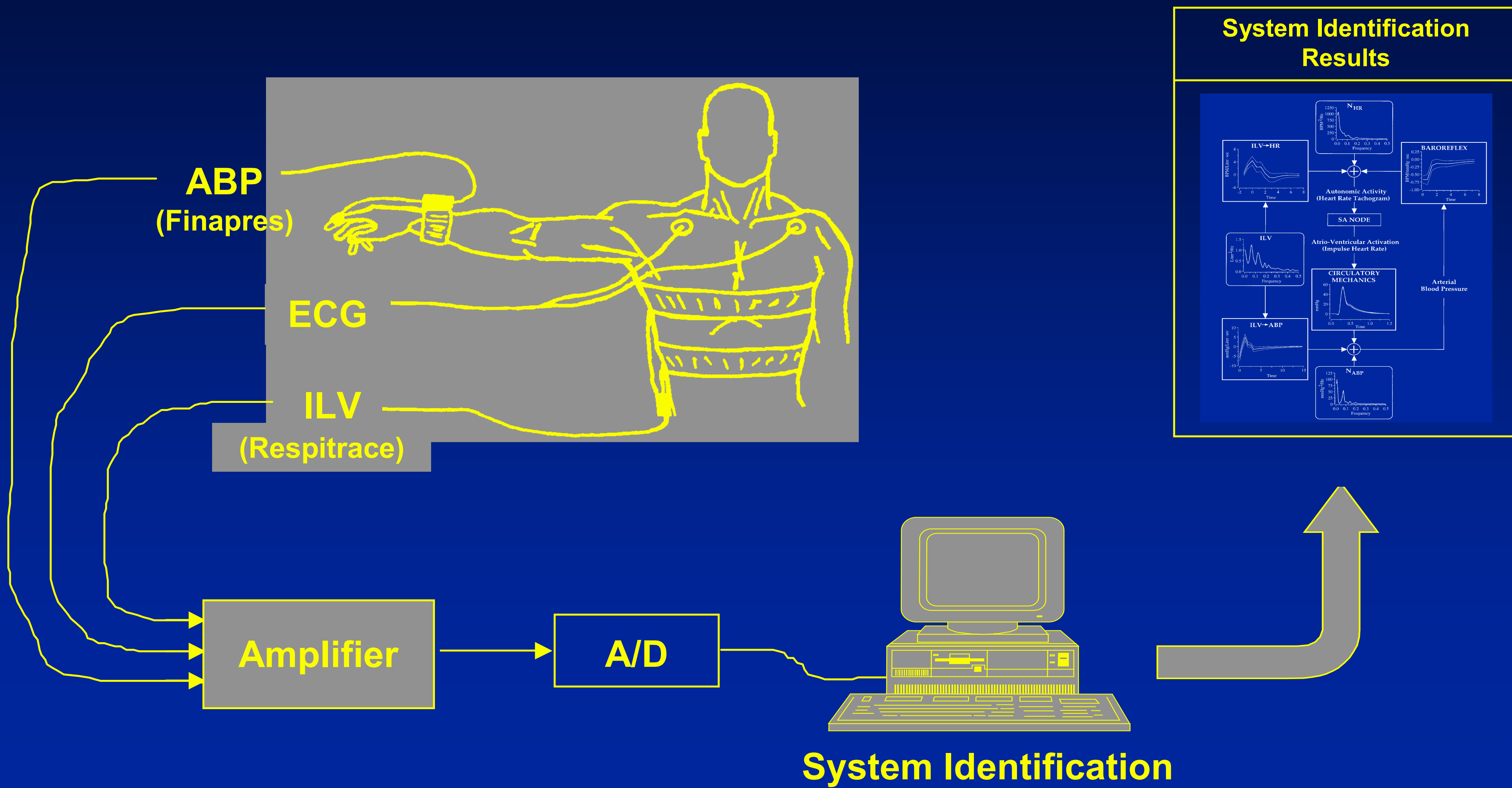
→

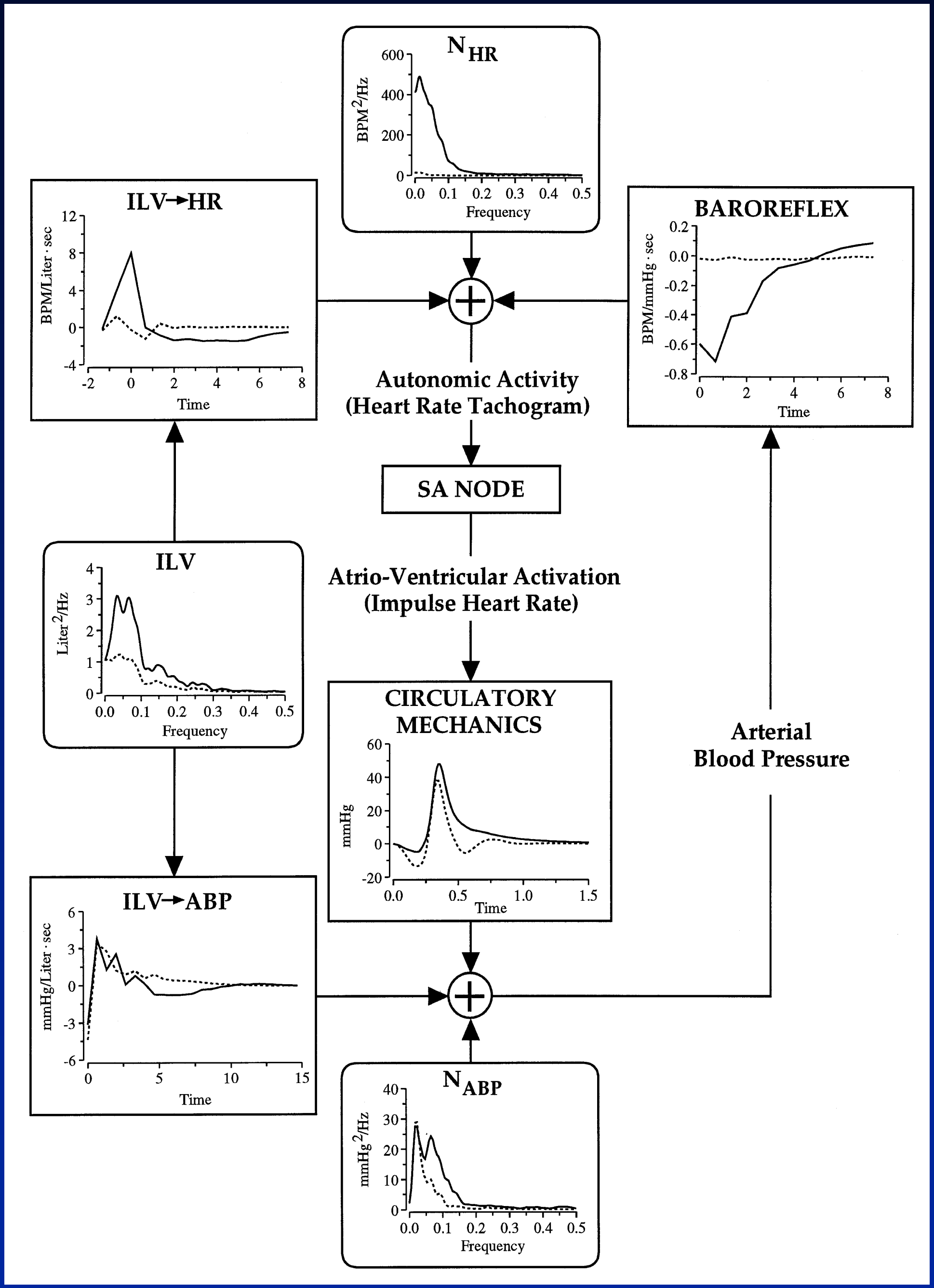
3 Days
Extensive
CV & Endocrine
Testing

Controlled Diet, NA, K and Fluid Intake

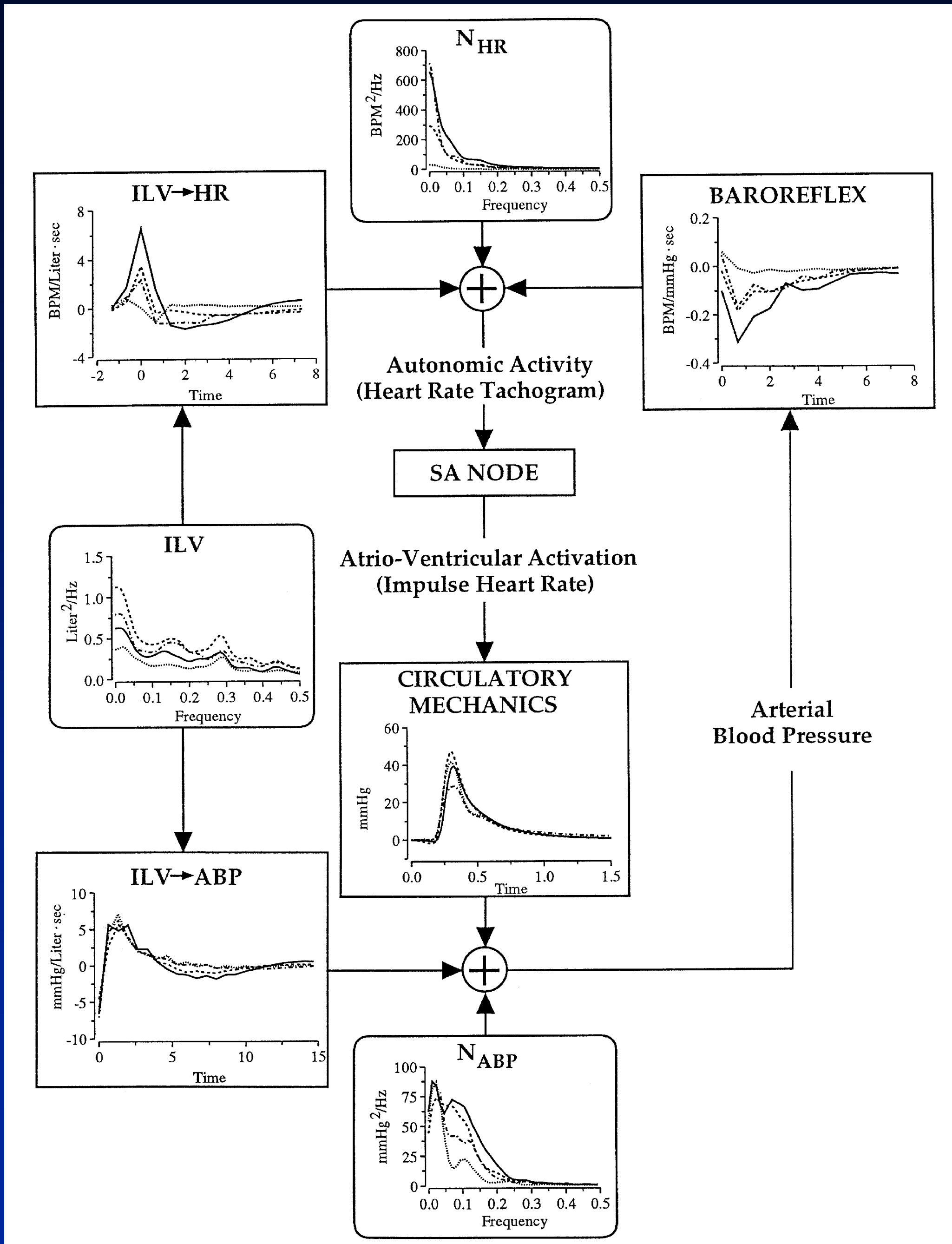
- Supine-Stand Tests
- AII Infusions
- Electrolytes
- Norepi Infusions
- Cardiovascular System ID
- T Wave Alternans
- Leg Compliance Studies
- Echocardiograms
- Others ...

Cardiovascular System Identification



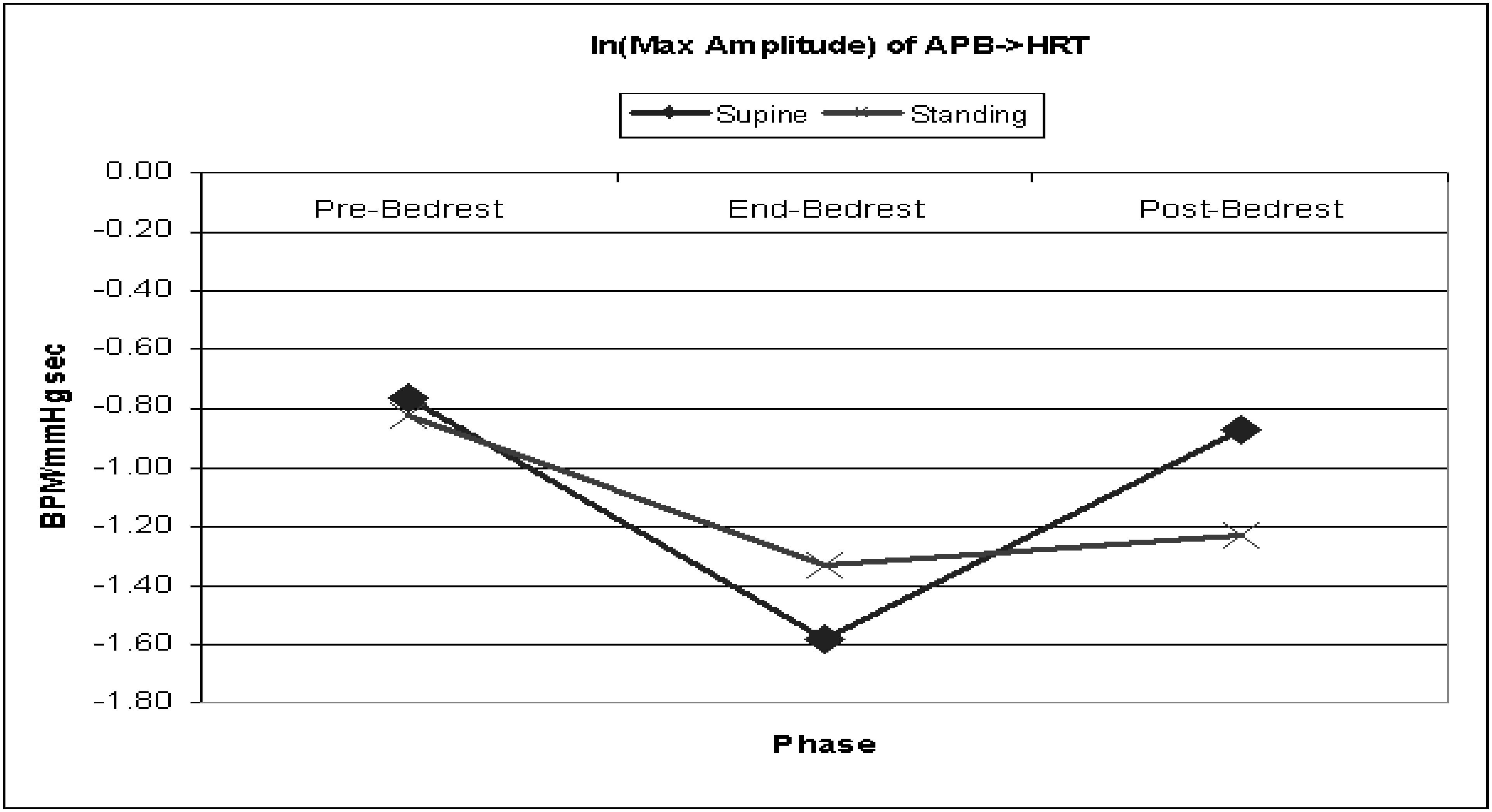


CSI
Effect of Autonomic Blockade

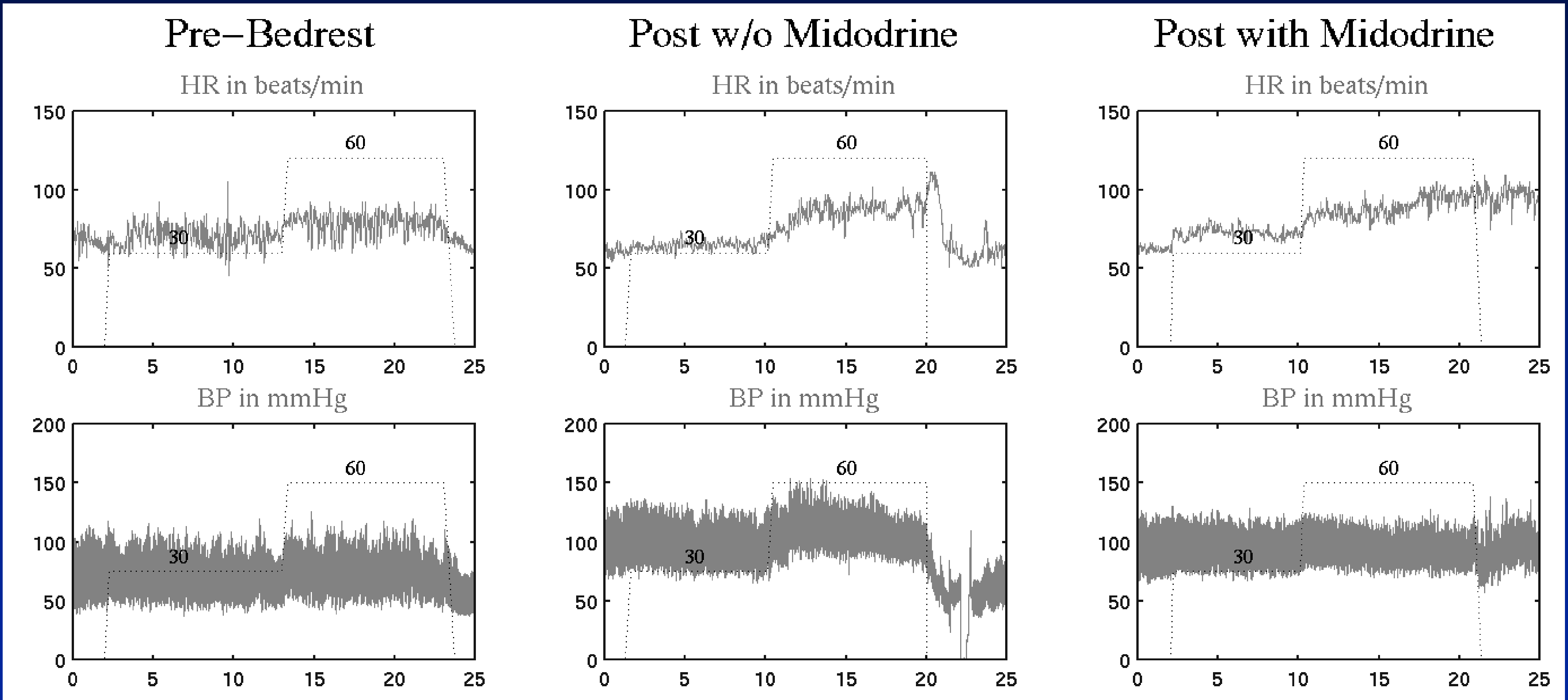


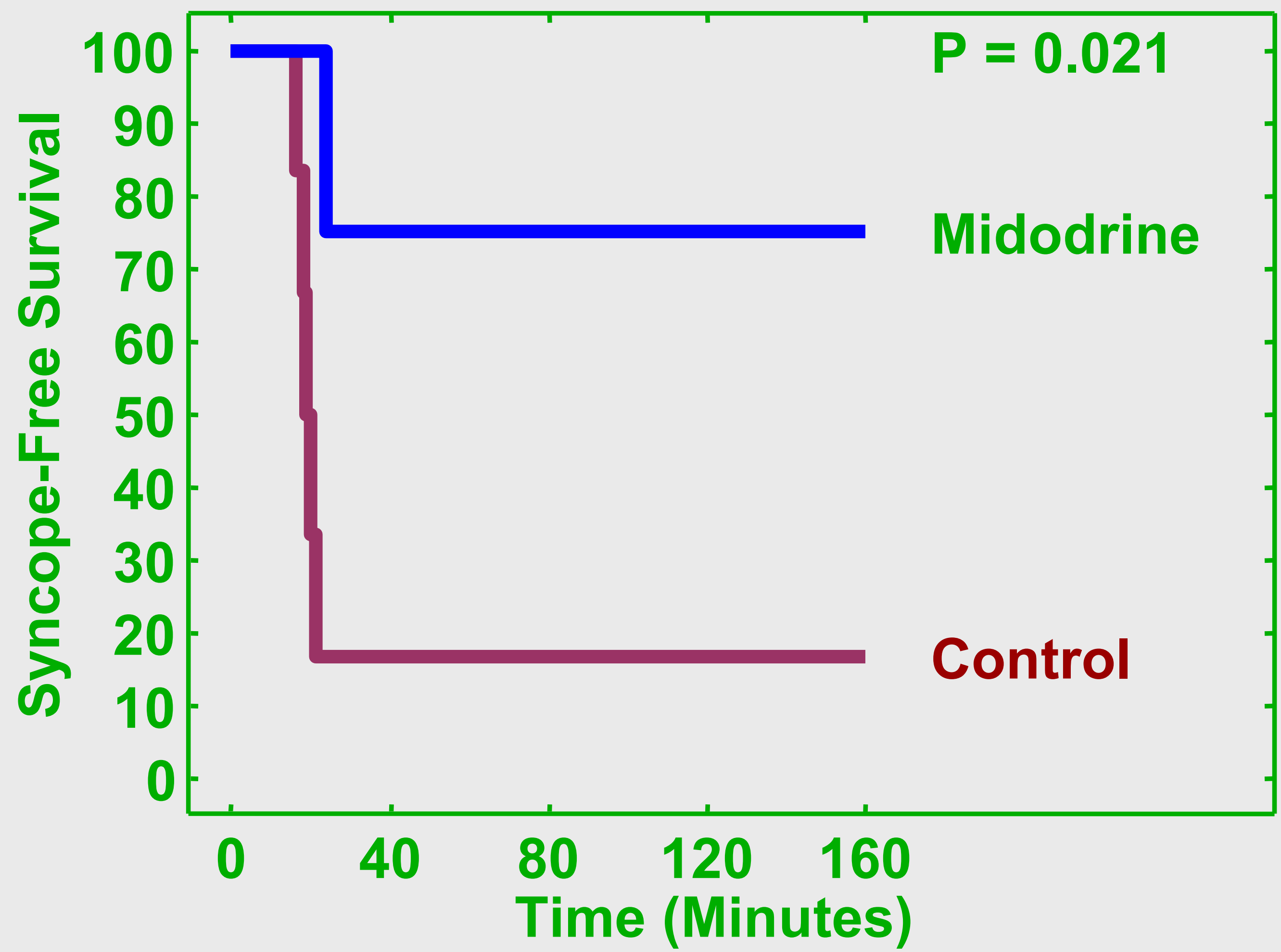
CSI
Effect of Autonomic Neuropathy

HR Barororeflex Sensitivity



Effect of Midodrine




P = 0.021
Midodrine
Control
Syncope-Free Survival
100
90
80
70
60
50
40
30
20
10
0
0
40
80
120
160
Time (Minutes)

Arrhythmias in Space

- Anecdotal reports of ventricular arrhythmias during spaceflight
- Runs of ventricular tachycardia recorded from members of Skylab and Mir
- Two Russian Mir cosmonauts reportedly brought back early due to heart rhythm disturbances
- Two primates died suddenly following landing
- No deaths from ventricular arrhythmias during space flight

Arrhythmias in Space

- It is not known whether or not spaceflight increases the risk of ventricular arrhythmias.
- If spaceflight does increase the risk of ventricular arrhythmias, it could be of concern for long term space flight such as during a mission to Mars.

Use of Microvolt T-Wave Alternans Testing to Reduce Risk of Sudden Cardiac Death

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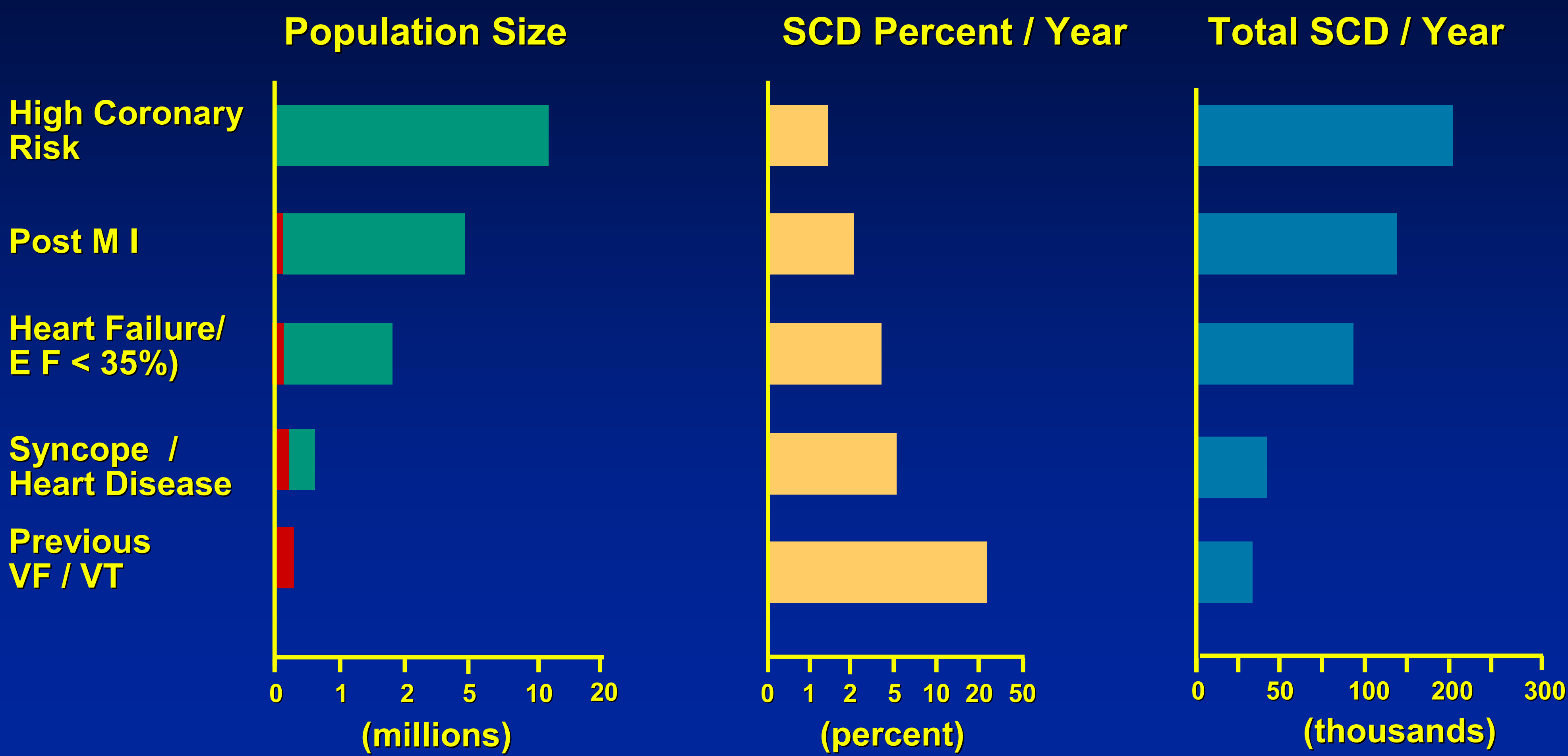
Sudden Cardiac Death

A Major Public Health Problem

- 1/2 of all cardiac deaths
- 1/7 of all deaths

High Risk Groups for SCD



Adapted from Myerburg

Heart Failure Patient With "Lightheadedness"

A 63-year-old man arrived in the hospital for suspected VT following a bout of lightheadedness. His history revealed a diagnosis of coronary artery disease, NYHA class II heart failure, previous coronary bypass graft surgery, and his LVEF was measured at 26%.

Patient with Non-Ischemic Dilated Cardiomyopathy

A 54-year-old woman arrived in the hospital following a syncopal episode. Her history revealed diagnoses of non-ischemic dilated cardiomyopathy, NYHA class I heart failure, and a previously measured LVEF was 25%.

VT in Patient with Acute MI

A 68 year old man presented with a chief complaint of three syncopal episodes on the day of

and cardiac enzymes confirmed acute myocardial infarction. Subsequent cardiac catheterization revealed two-vessel CAD and normal ventricular function.

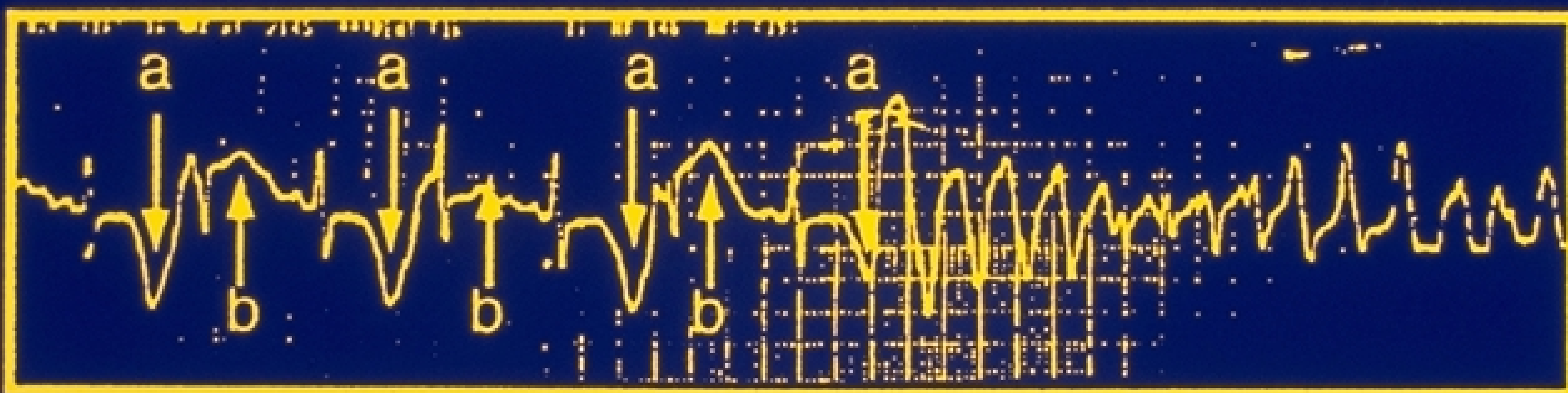
Patient with Prior MI and Renal Failure

A 64 year old man with a 20 year history of renal failure, and a history of an MI 12 years prior to admission, presented with a new anterior myocardial infarction. His LVEF was 40% and he had NYHA class II heart failure.

Syncope & Family History of SCD

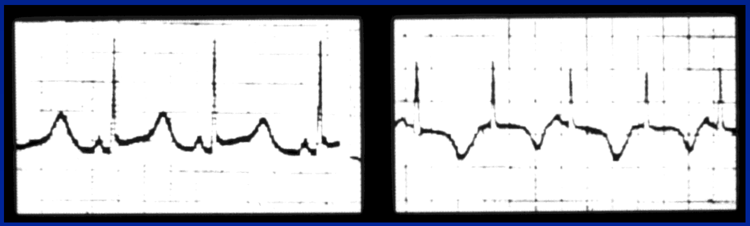
A 25-year-old male was evaluated for abrupt loss of consciousness. A family history of sudden death prompted the need for further evaluation. His LVEF was normal.

Electrical Alternans Preceding Ventricular Fibrillation



Historical References

1. Herring H: Experimentelle Studien an Saugetieren uber das Electrocardiogramm Ztchr fd ges exper Med 1909; 7:363.
2. Lewis T: Notes upon alternation of the heart. Quart J Med 1910; 4:141-144.
3. Kleinfeld M, Rozanski J: Alternans of the ST segment in Prinzmetal's angina. Circ 1977; 55:574-577.
4. Schwartz PJ, Malliani: A. Electrical alternation of the T-wave: Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. AM Heart J 1975; 89:45-50.
5. Reddy CVR, Kiok JP, Khan RG, El-Sherif N: Repolarization alternans associated with alcoholism and hypomagnesemia. Am J Cardiol 1984; 53:390-391.



Relaxed **Emotional Excitement**

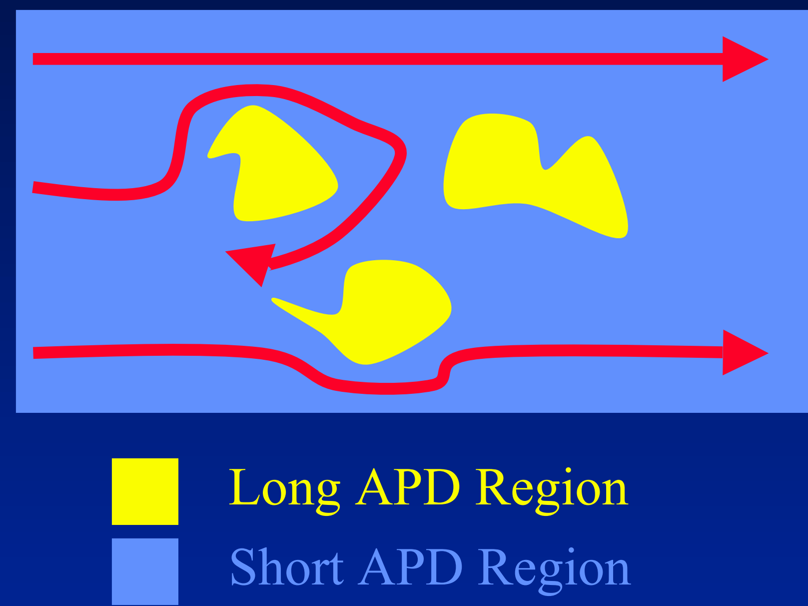
(Schwartz & Malliani. Am Heart J 1975; 89:45-50)

Historical References

- Kalter HH (Electrical Alternans, N. Y. State J. M., 1948) reviewed 46 cases of electrical alternans reported in the world literature
- Incidence approximately 1 in 1000 ECG's
- Mortality 61%

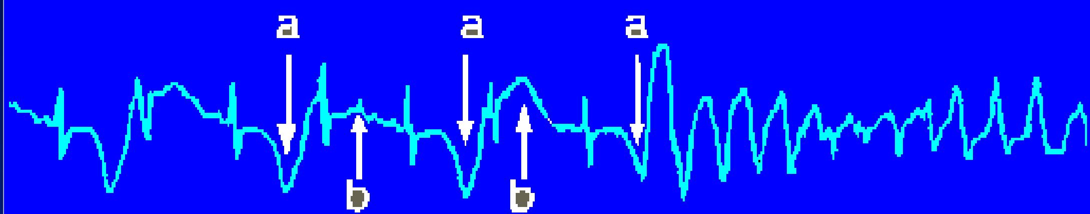
Mechanism Linking TWA to Ventricular Arrhythmias

Action Potential Alternans Leads to T-Wave Alternans

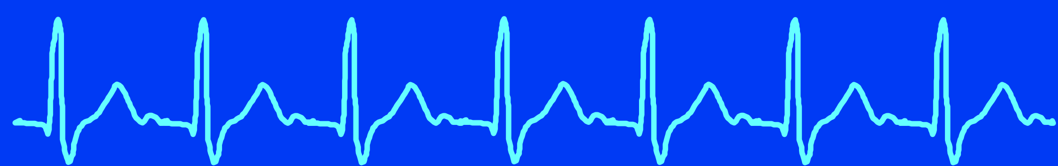


Spatially Discordant Alternans Leads to Dispersion of Recovery, Wave Front Fractionation, and Reentry

T-Wave Alternans

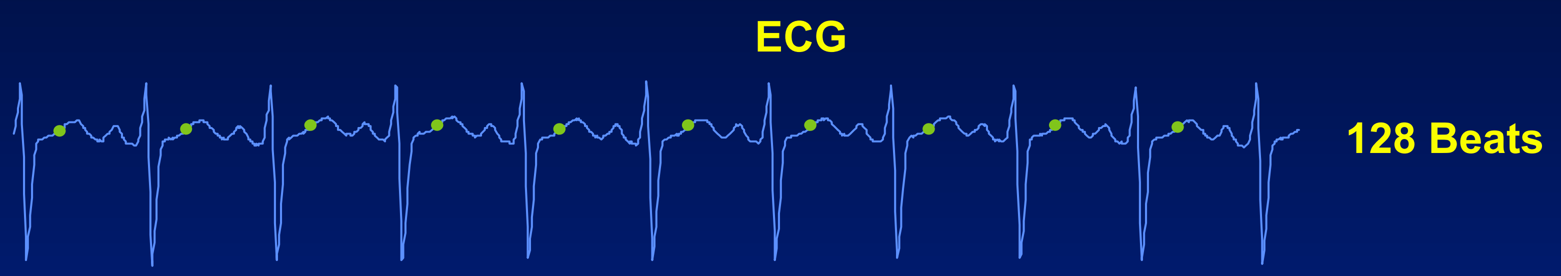


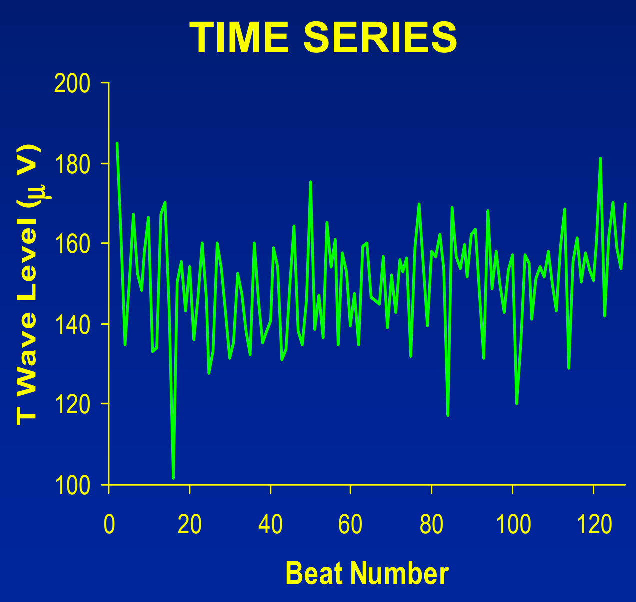
Visible



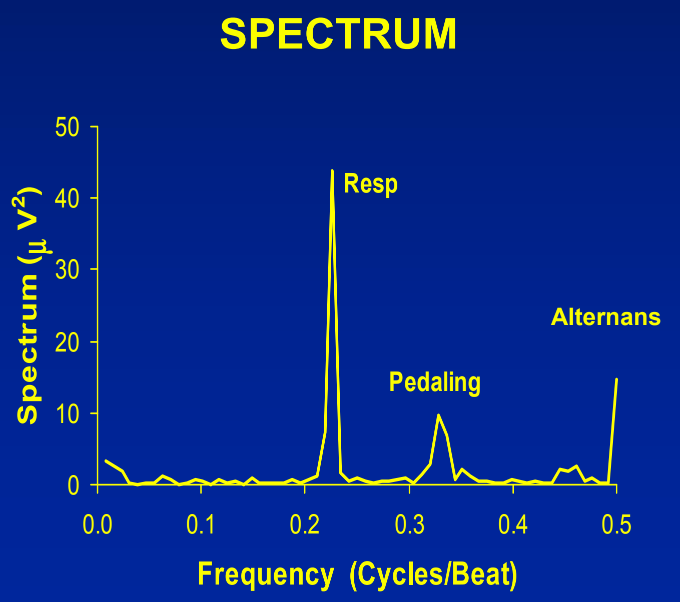
Microvolt Level

T-Wave Alternans Measurement: Spectral Method

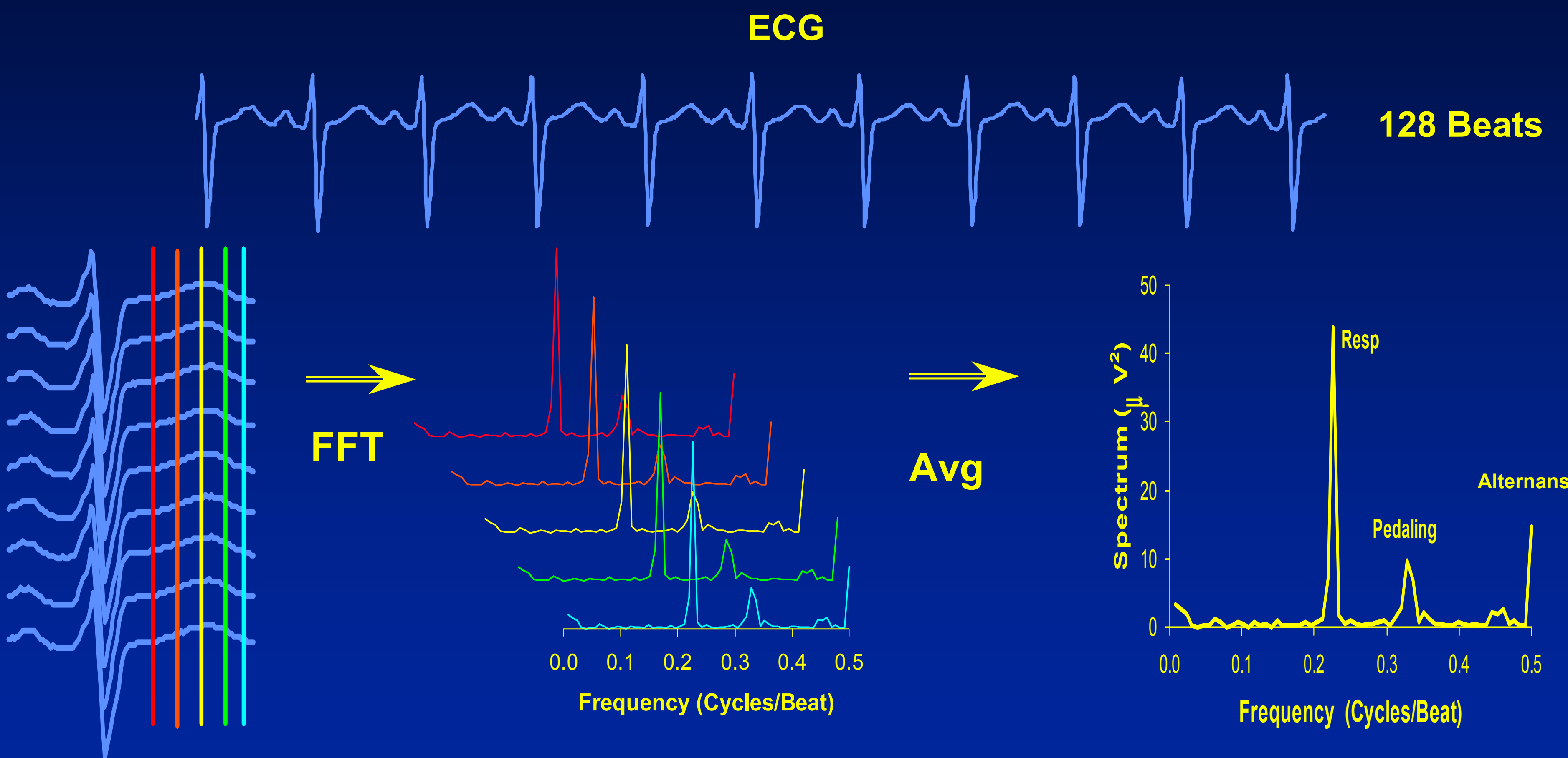




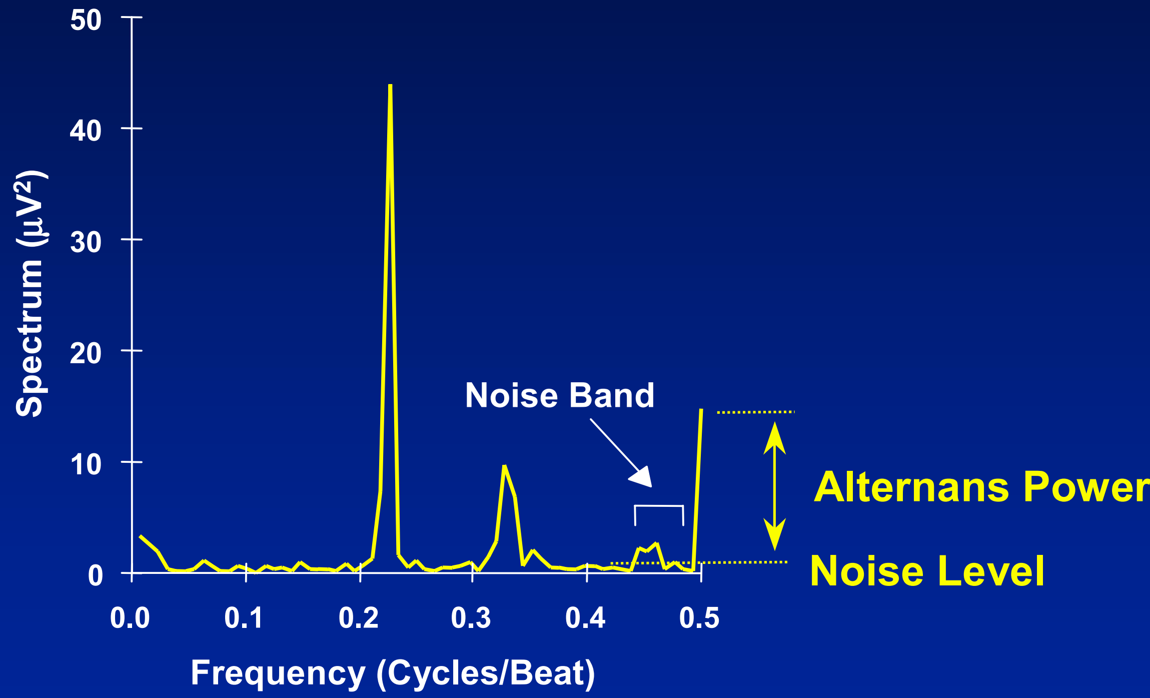
FFT



T-Wave Alternans Measurement: Spectral Method



T-Wave Alternans Measurement: Spectral Measures



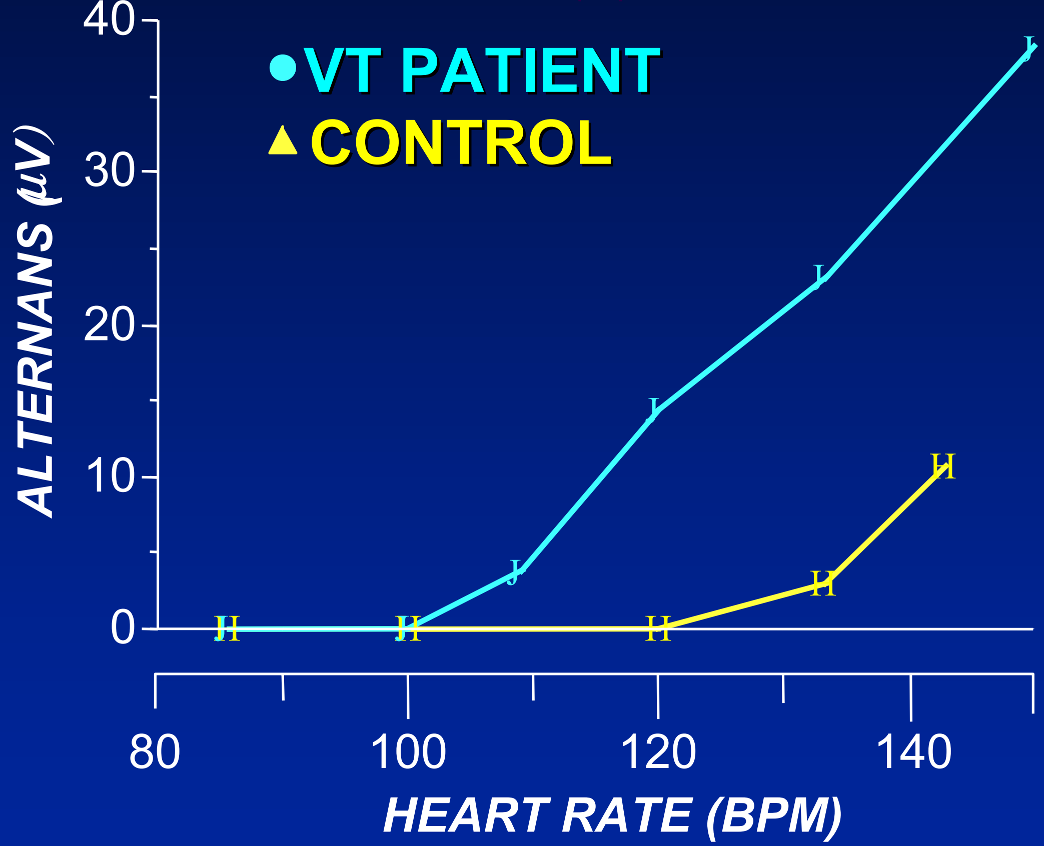
Alternans Voltage (V_{alt})

V_{alt} = (Alternans Power)$^{1/2}$

Alternans Ratio (k)

$$k = \frac{\text{Alternans Power}}{\text{Noise Std. Dev.}}$$

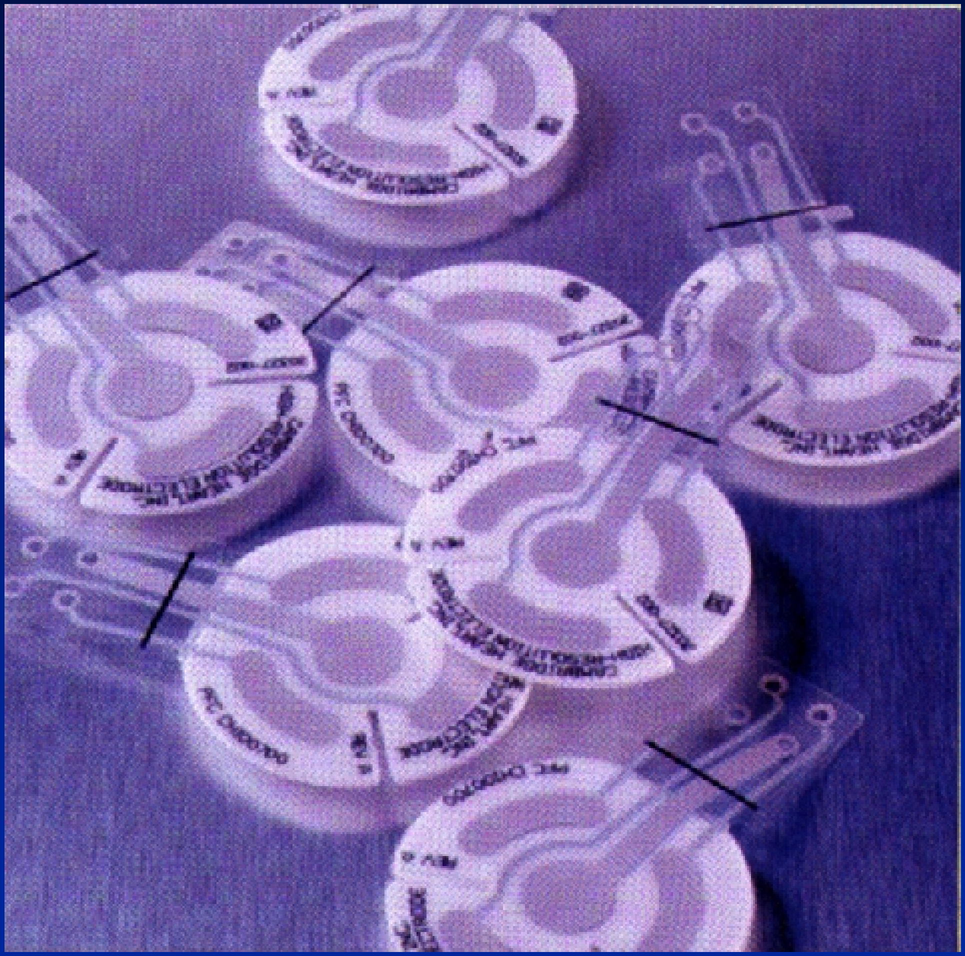
Heart Rate Dependence of TWA



Rosenbaum, et al

Measurement of T-Wave Alternans During Exercise Stress

Micro-V Alternans Sensors



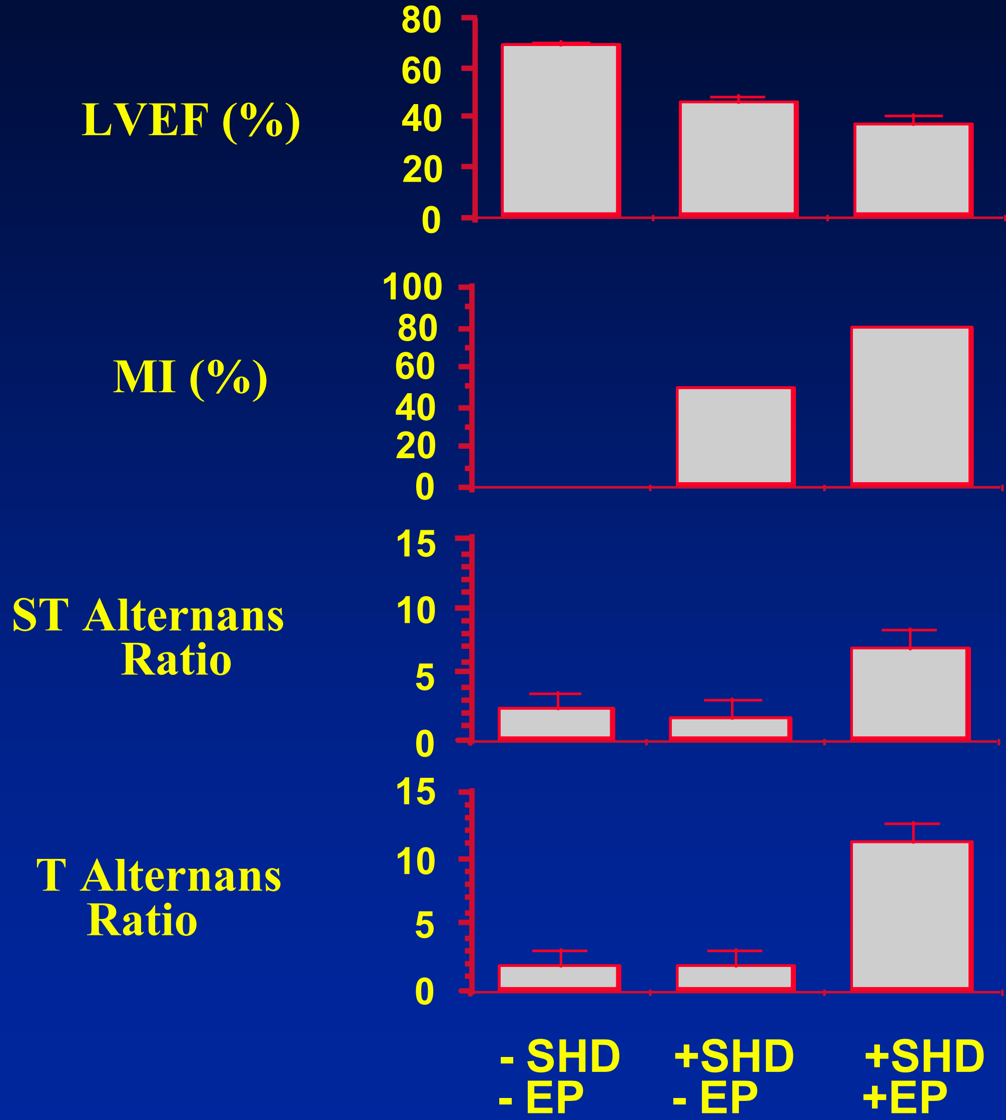
MGH/MIT Clinical Study

- 83 consecutive patients referred to EP lab at MGH
- Alternans vs EP and arrhythmia-free survival
- Alternans measured during atrial pacing

- Patient Characteristics:
  - Age (years) — 57 ± 16
  - Indication for Study
    - Cardiac Arrest — 20%
    - Sustained Ventricular Tachycardia — 31%
    - Syncope — 22%
    - Supraventricular Arrhythmias — 18%
    - Other — 8%
  - Heart Disease
    - Coronary Artery Disease — 64%
    - Dilated Cardiomyopathy — 8%
    - Mitral Valve Prolapse — 4%
    - No Organic Heart Disease — 24%

Rosenbaum, Jackson, Smith, Garan, Ruskin, Cohen. NEJM 1994;330:235-41.

Electrical Alternans Versus Electrophysiologic Testing

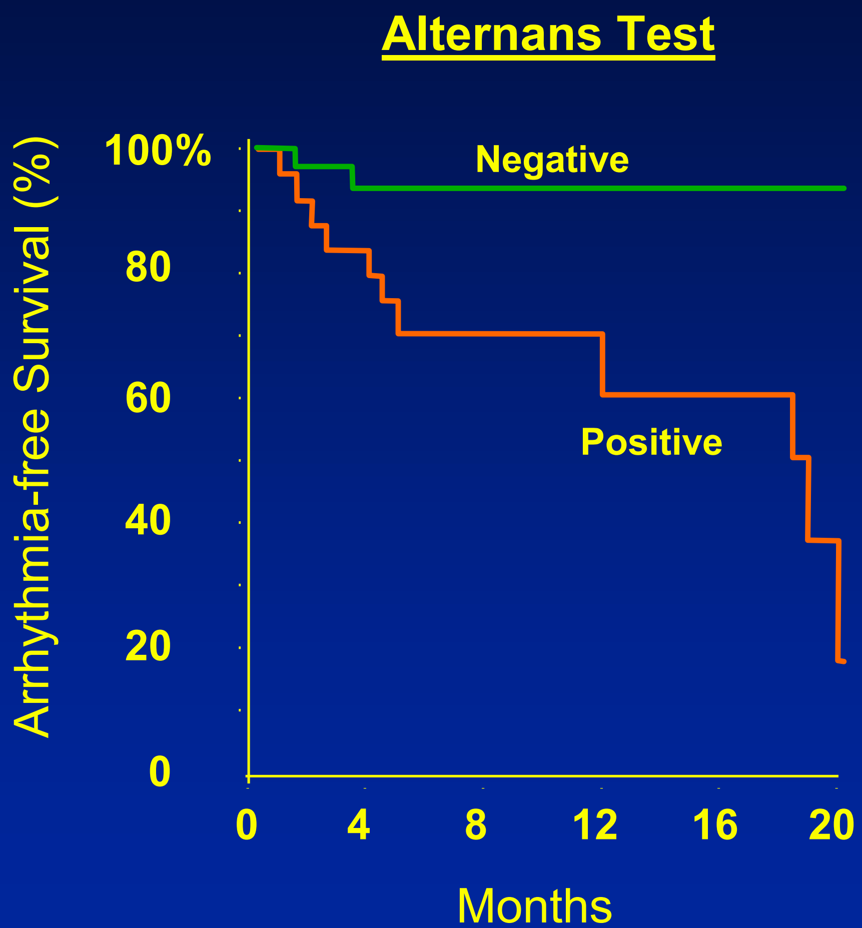


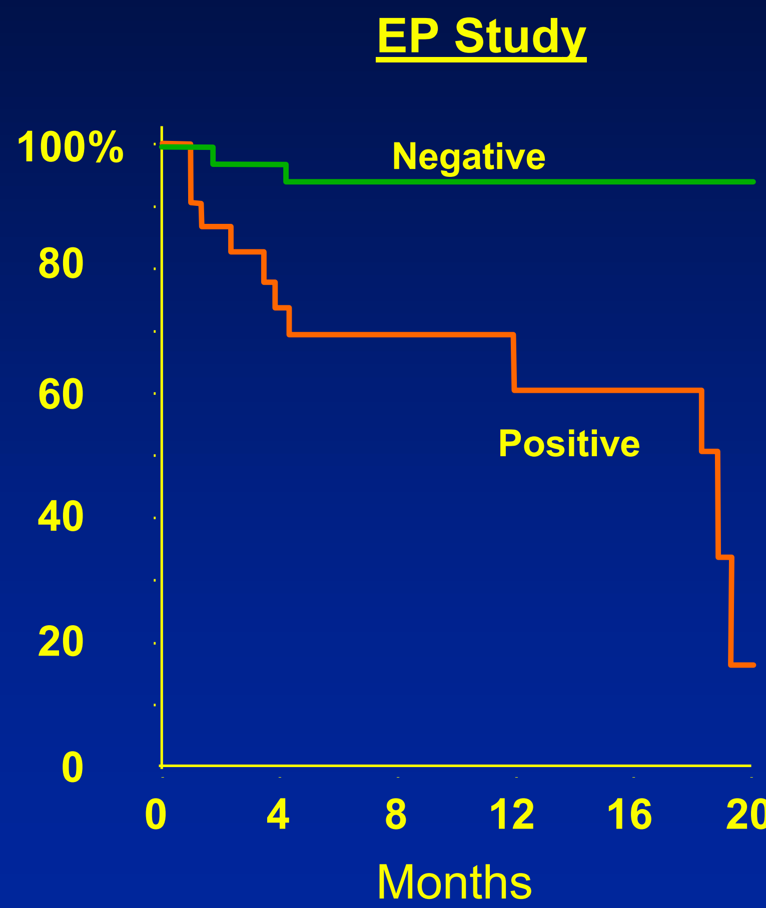
SHD: Structural Heart Disease

Rosenbaum et al., New England Journal of Medicine, 330, 235-241, 1994.

MGH / MIT Results

Arrhythmia Free Survival





Rosenbaum, Jackson, Smith, Garan, Ruskin and Cohen N Engl J Med 1994;330:235-241

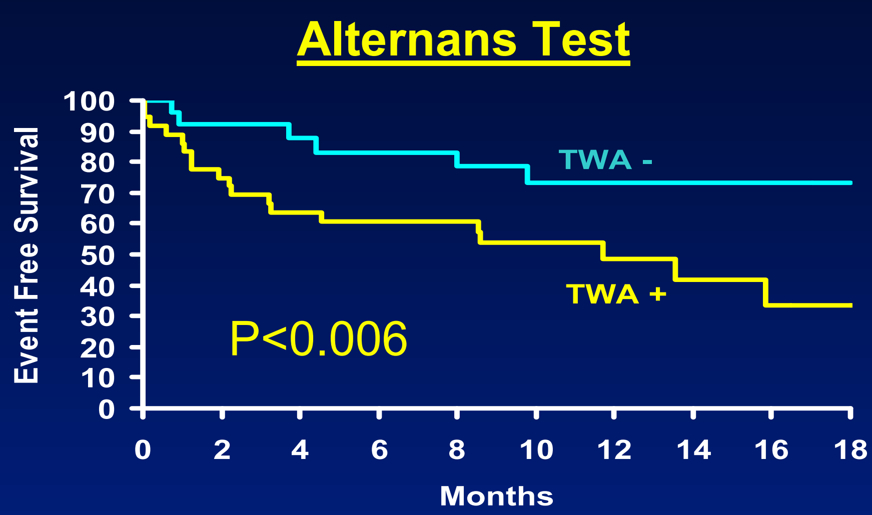
Frankfurt ICD Study

- 95 consecutive patients receiving ICD's
- Risk stratification prior to implant:
  - TWA, EPS, LVEF, BRS, SAECG, HRV, QT Dispersion, QTVI, Mean RR, NSVT
- Endpoint: First appropriate ICD firing

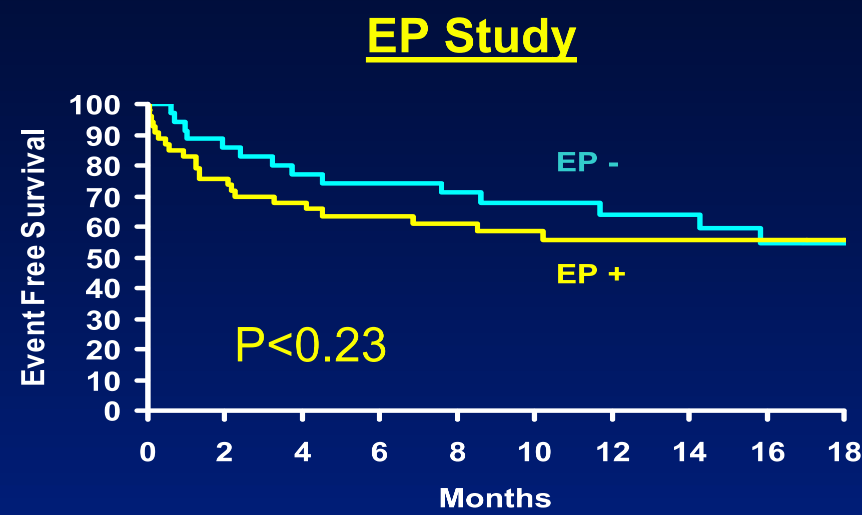
- Patient Characteristics
  - Age (years) 60±10
  - Ejection Fraction (%) 36±14
  - Index Arrhythmia
    - Ventricular Fibrillation 40%
    - VT/VF 4%
    - VT 48%
    - Nonsustained VT with Syncope 8%
  - Heart Disease
    - Coronary Artery Disease 75%
    - Dilated Cardiomyopathy 17%
    - Other 3%
    - None 5%

Hohnloser, Klingenheben, Li, Zabel, Peetermans, and Cohen. JCE 1998; 9: 1258-1268.

Frankfurt ICD Study Results



Relative Risk 2.5



Relative Risk 1.0

- 41 first appropriate ICD firings (34 for VT, 7 for VF)
- TWA (relative risk 2.5, $p < 0.006$) and LVEF (relative risk 1.4, $p < 0.04$) were the only statistically significant univariate predictors of appropriate ICD firing during follow-up.
- Cox regression analysis revealed that TWA was the only statistically significant independent predictor of appropriate ICD firing.

Multi-Center Regulatory Study

- 337 patients referred for EP study, 9 US Centers
- Endpoints: Ventricular tachyarrhythmic events(VTE), VTE plus Total Mortality

- Patient Characteristics

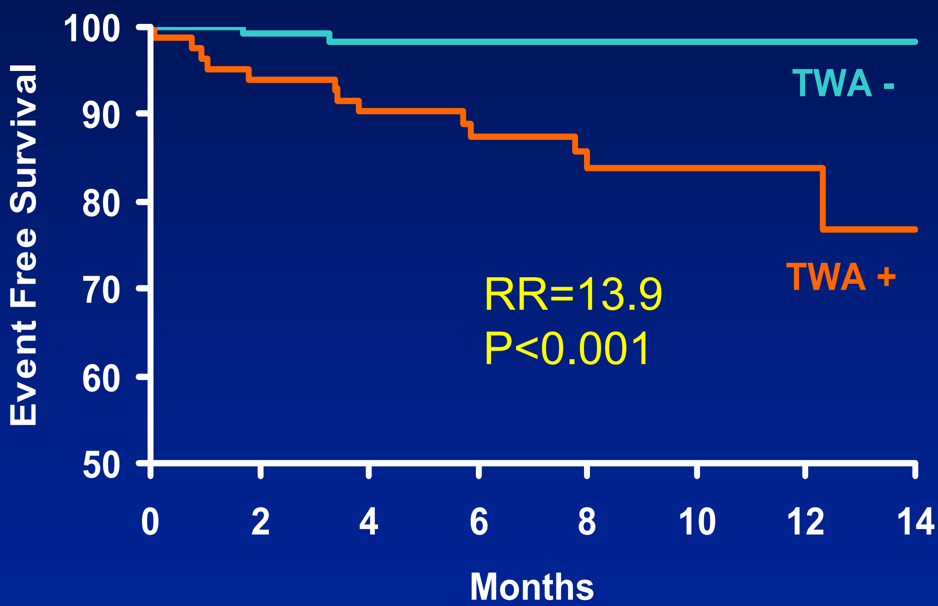
– Age (years)	56±16
– Ejection Fraction (%)	44±18
– Indication for Study	
• Cardiac Arrest	5%
• Sustained Ventricular Tachycardia	14%
• Syncope/Presyncope	41%
• Supraventricular Tachycardia	31%
• Other	9%
– Heart Disease	
• Coronary Artery Disease	41%
• Other Structural Heart Disease	29%
• No Structural Heart Disease	30%
– Congestive Heart Failure	34%

Gold MR, et al. (FDA-Cleared Labeling, Cambridge Heart, Inc. K No. 983102). JACC, in press.

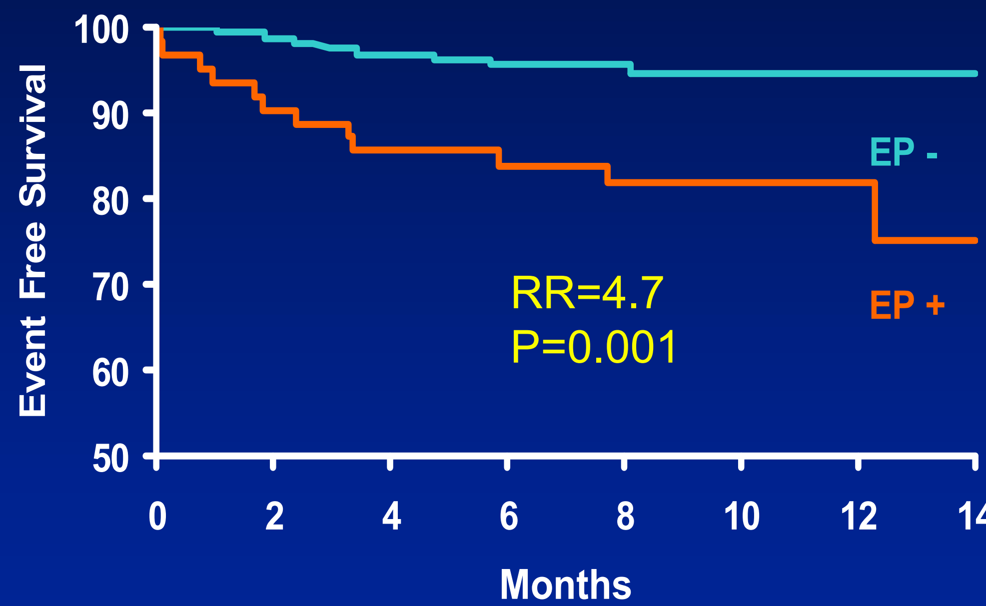
Multi-Center Regulatory Study

Prediction of VT/VF, ICD Firing and Total Mortality

Alternans Test



EP Study



Gold MR, et al. (FDA-Cleared Labeling, Cambridge Heart, Inc. K No. 983102). JACC, in press.

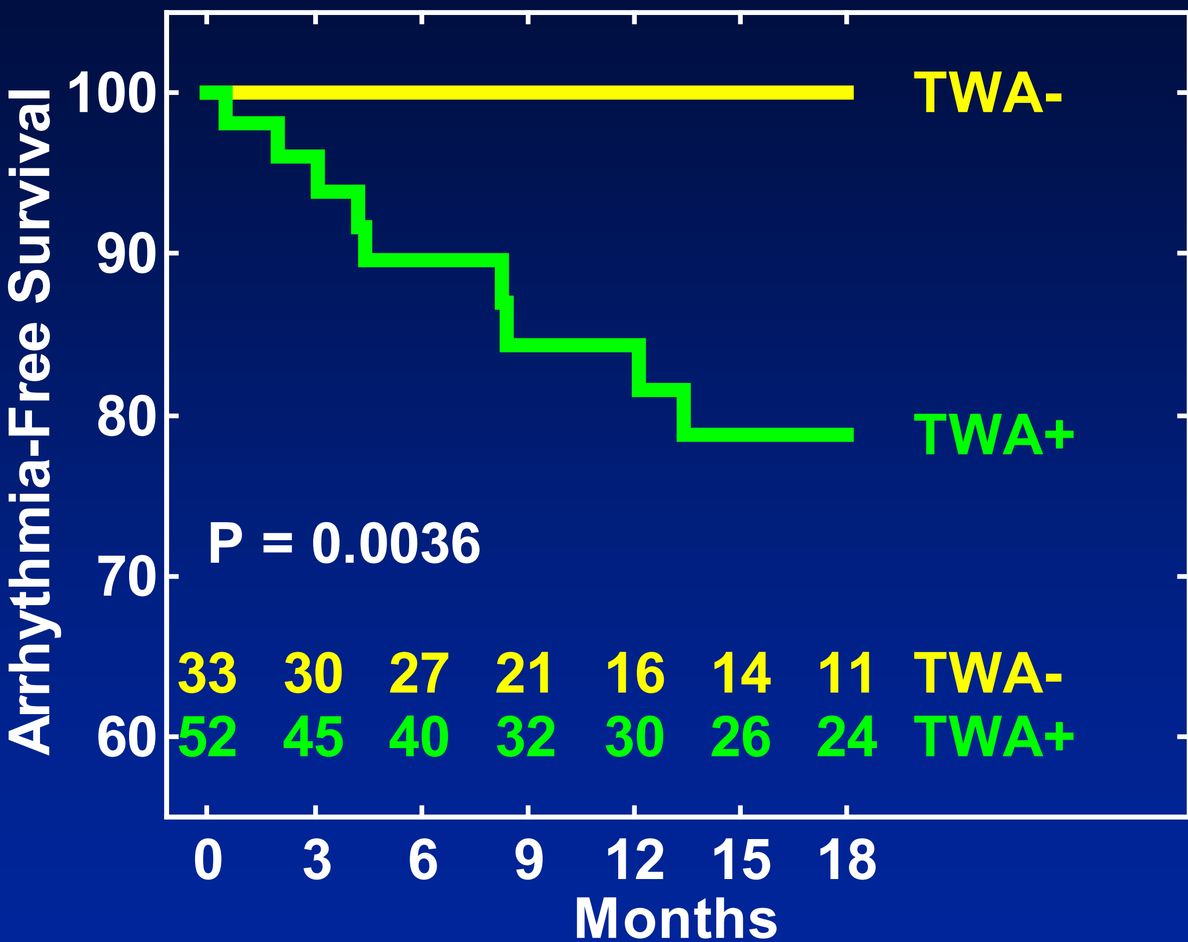
Frankfurt CHF Study

- 107 consecutive patients with NYHA class II and III heart failure, no recent MI (6 weeks), and no prior history of VT or VF
- TWA, EF, SAECG, Mean RR, HRV, NSVT, BRS tests performed
- End-point Ventricular Tachyarrhythmic Events (VTE = VT, VF or SCD)

- Patient Characteristics
  - Age (years) 56±10
  - Ejection Fraction (%) 28±07
  - Heart Disease
    - Coronary Artery Disease 67%
    - Dilated Cardiomyopathy 33%
  - ACE Inhibitors 93%
  - Beta Blockers 42%

Klingenheben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. The Lancet 2000; 356: 651-652.

Frankfurt CHF Study Results



- 13 Endpoint Events
- Sensitivity 100%
- PPV 21%
- TWA the only statistically significant predictor

Klingenheben T, Cohen RJ, Peetermans JA,, Hohnloser SH. AHA, 1998Klingenheben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. The Lancet 2000; 356: 651-652.

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Ikeda Post-MI Study

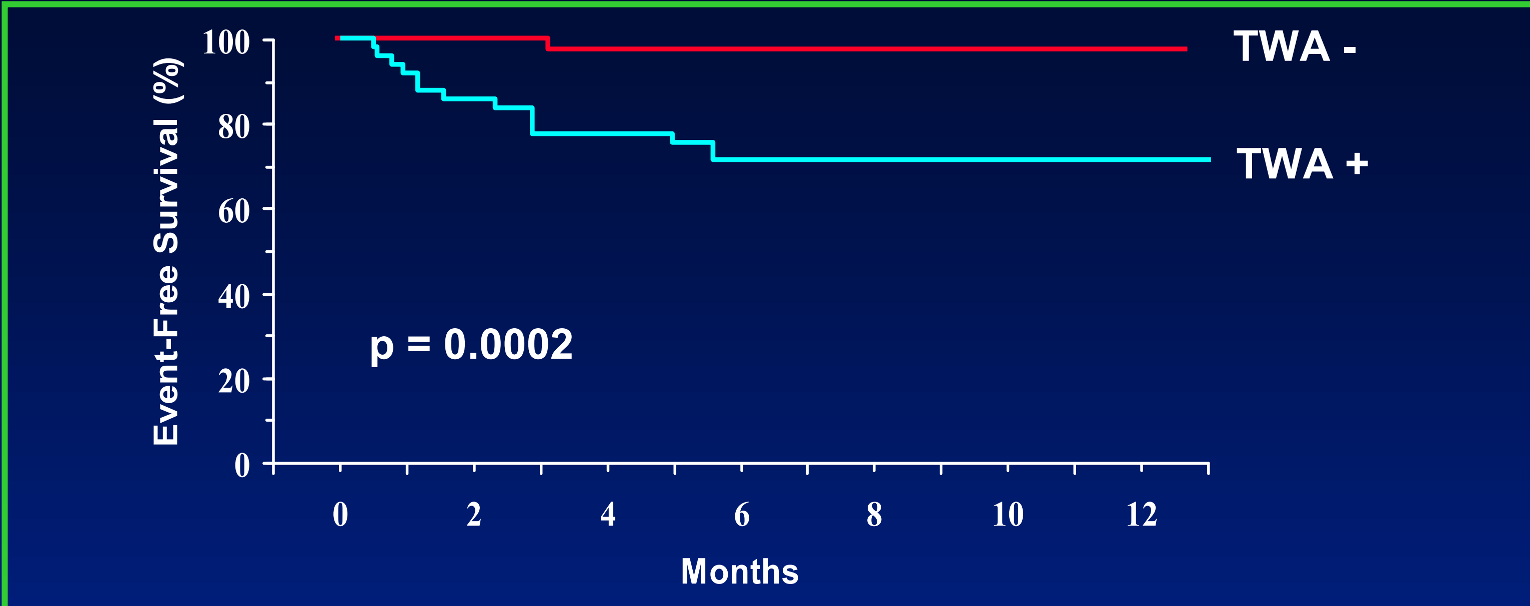
- 119 consecutive patients with acute MI
- TWA, SAECG, and EF measured
- Endpoints: sustained VT, VF, sudden death

- Patient Characteristics
  - Age (years) 60±9
  - Ejection Fraction (%) 49±9
  - Myocardial Infarction
    - Anterior 49%
    - Lateral 17%
    - Inferior 34%
  - Primary PTCA 98%

- TWA test at 20±6 (7 to 30 days) post-MI

Ikeda, Sakata, Takami, Kondo, Tezuka, Nakae, Noro, Enjoji, Abe, Sugi, Yamaguchi. **JACC** 2000;35:3:722-30

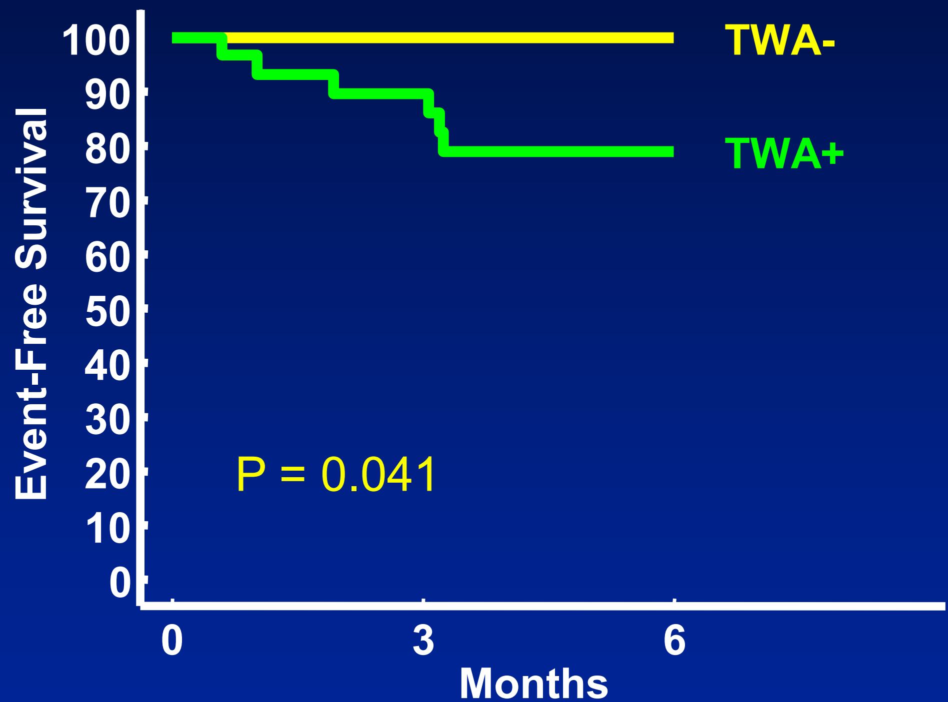
Ikeda Post-MI Study Results



- TWA had the highest univariate relative risk (16.8) compared to SAECG (5.7) and EF (4.7).
- TWA had the highest sensitivity (93%) compared to SAECG (53%) and EF (60%).
- TWA negative patients had the lowest one-year event rate (2%) compared to SAECG (9%) and EF (8%).
- TWA positive patients had a one-year event rate of 28%; the low EF subgroup of these patients had a one-year event rate of 39%.

Non-Ischemic DCM Study Results

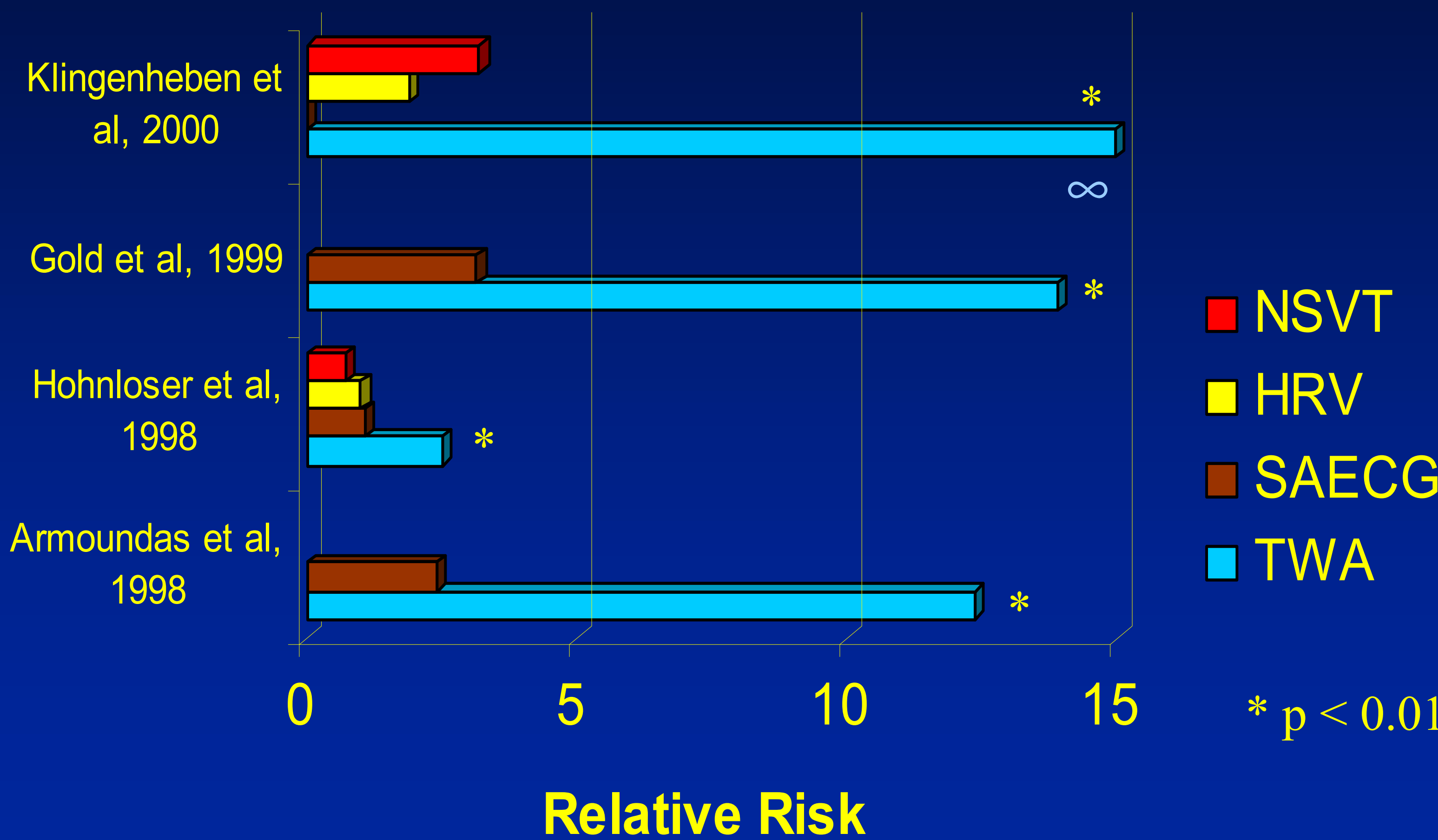
Preliminary Results in 56 patients



- **56 non-ischemic dilated cardiomyopathy patients**
- **Endpoints: VT, VF, SCD**
- **All events among TWA+ patients**

Klingenheben T, Credner SC, Bender B, Cohen RJ, Hohnloser SH. NASPE, 1999.

Prediction of Arrhythmia-Free Survival



Event Rates Among TWA+ and EP+ Patients

Study	Patient Population	Follow-Up (months)	TWA+	EP+
Rosenbaum, et al NEJM, 1994	EP	20	81%	~81%
Ikeda, et al JACC, 2000	Post MI	12	28%	
Gold MR, et al FDA, 1999	EP	13	23%	25%
Gold MR, et al FDA, 1999 JACC, in press	Known or Suspected Ventricular Arrhythmia (EP)	13	26%	25%
Bloomfield, et al Circ, 1999 (abs)	Syncope (EP)	13	19%	21%
Klingenheben, et al The Lancet, 2000	CHF	18	21%	
Klingenheben, et al PACE, 1999 (abs)	DCM	6	21%	
Buxton, et al NEJM, 2000	Prior MI, EF $\leq$ 0.40, NSVT	24		18%

Event Rates Among TWA- and EP- Patients

Study	Patient Population	Follow-Up (months)	TWA-	EP-
Rosenbaum, et al NEJM, 1994	EP	20	6%	~6%
Ikeda, et al JACC, 2000	Post MI	12	2%	
Gold MR, et al FDA, 1999	EP	13	2%	5%
Gold MR, et al FDA, 1999 JACC, in press	Known or Suspected Ventricular Arrhythmia (EP)	13	3%	8%
Bloomfield, et al Circ, 1999 (abs)	Syncope (EP)	13	3%	6%
Klingenheben, et al The Lancet, 2000	CHF	18	0%	
Klingenheben, et al PACE, 1999 (abs)	DCM	6	0%	
Buxton, et al NEJM, 2000	Prior MI, EF$\leq$ 0.40, NSVT	24		12%

Observations

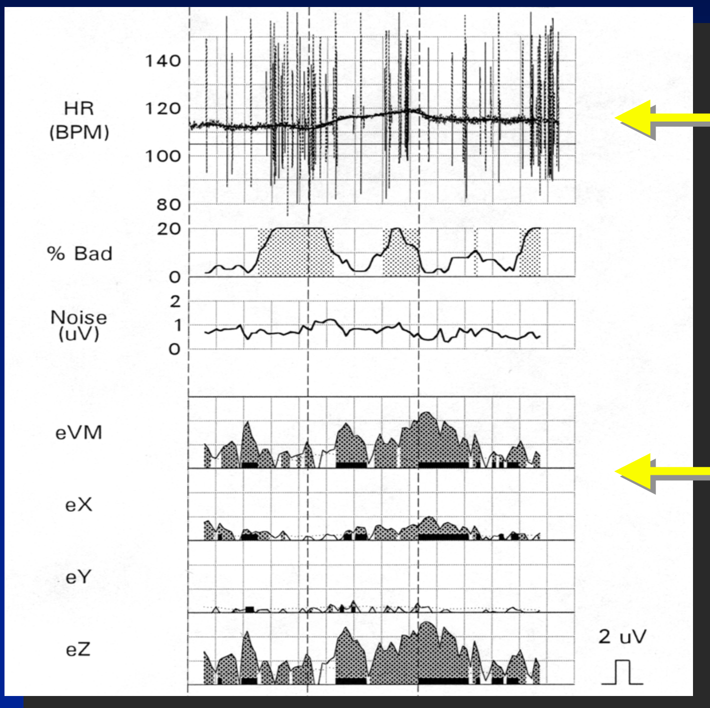
In a variety of populations:

- Ventricular tachyarrhythmic event rates among TWA+ patients are elevated and comparable to event rates among EP+ patients.
- Ventricular tachyarrhythmic event rates among TWA- patients are reduced to a level below that of EP- patients.

Clinical Applications

- History Indicating Increased Risk of Sustained Ventricular Arrhythmias
  - Syncope, Presyncope, Palpitations, Non-Sustained VT, Family History, VT or VF Associated with Transient or Reversible Cause
- Left Ventricular Dysfunction
  - Heart Failure, Cardiomyopathy, Reduced Ejection Fraction
- Prior Myocardial Infarction
- Patients Undergoing Electrophysiology Study

Heart Failure Patient With "Lightheadedness"



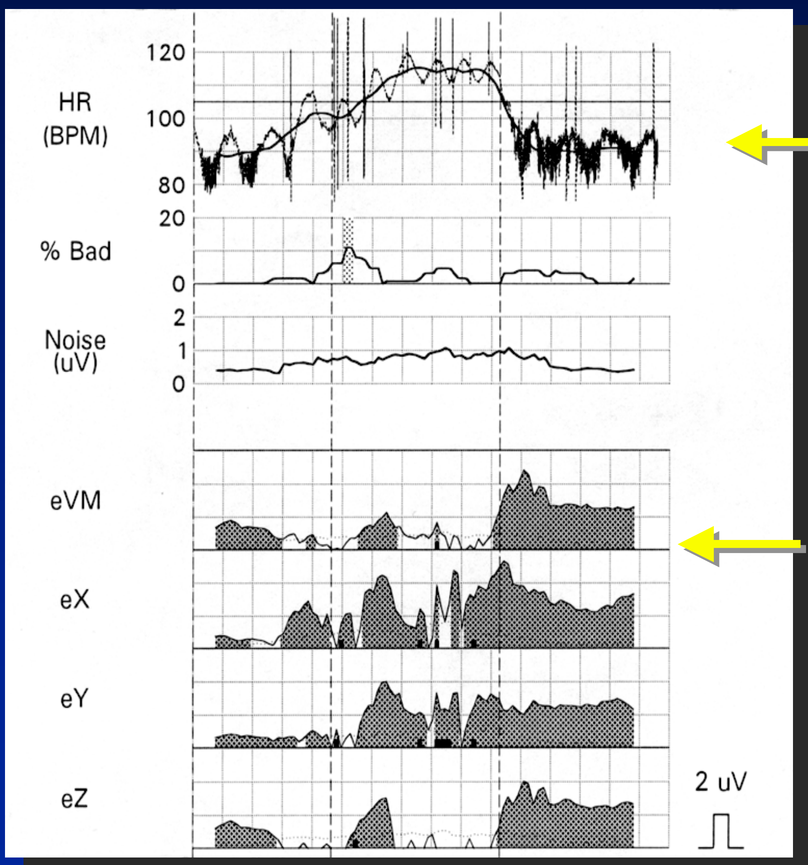
Heart Rate

T-Wave Alternans

A 63-year-old man arrived in the hospital for suspected VT following a bout of lightheadedness. His history revealed a diagnosis of coronary artery disease, NYHA class II heart failure, previous coronary bypass graft surgery, and his LVEF was measured at 26%.

The results of both T-wave alternans and EPS were positive. He was implanted with an ICD, and the device fired appropriately eight weeks later in response to ventricular tachyarrhythmia.

Patient with Non-Ischemic Dilated Cardiomyopathy



Heart Rate

T-Wave Alternans

A 54-year-old woman arrived in the hospital following a syncopal episode. Her history revealed diagnoses of non-ischemic dilated cardiomyopathy, NYHA class I heart failure, and a previously measured LVEF was 25%.

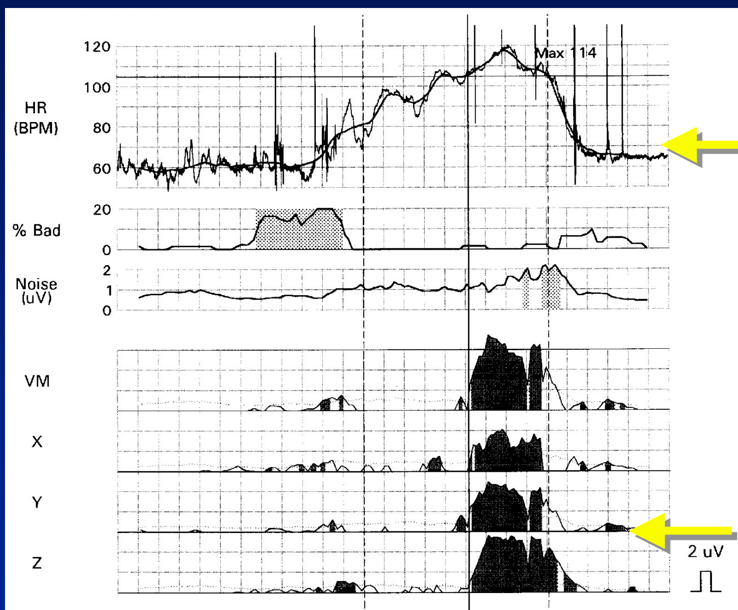
Patient tested T-wave alternans positive. She received an ICD despite being non-inducible in EPS. Three months post-implantation, the patient experienced a ventricular tachyarrhythmia terminated by ICD shock.

VT in Patient with Acute MI

A 68 year old man presented with a chief complaint of three syncopal episodes on the day of presentation. ECG revealed VT at a rate of 150 bpm and cardiac enzymes confirmed acute myocardial infarction. Subsequent cardiac catheterization revealed two-vessel CAD and normal ventricular function.

Six weeks post MI patient had a positive T wave alternans test, but refused EPS and further work-up. Patient subsequently presented to the hospital complaining of an episode of lightheadedness and confusion not associated with slurred speech, weakness or chest pain. Cardiac enzymes were negative. At this time patient agreed to EPS which was positive for inducible VT, and an ICD was implanted.

Patient with Prior MI and Renal Failure



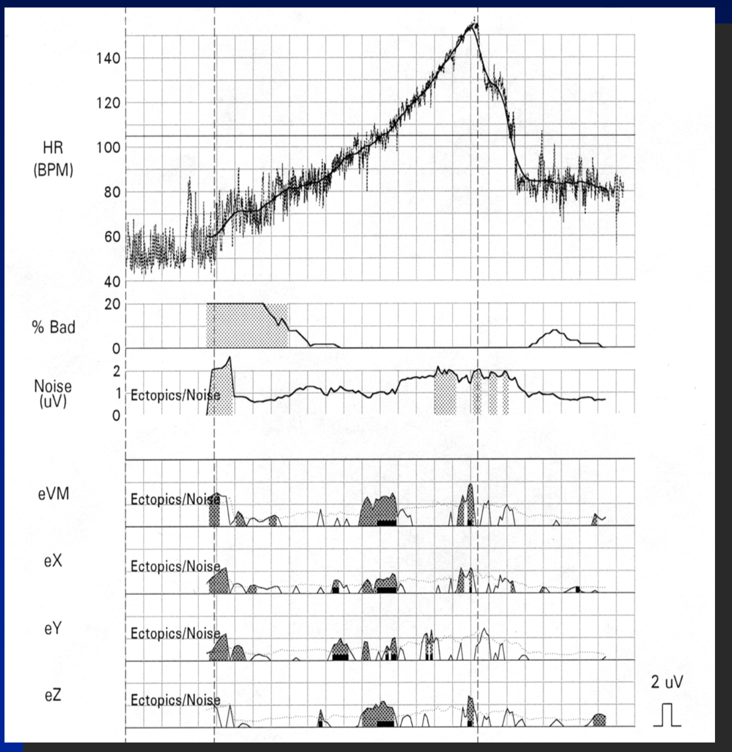
Heart Rate

T-Wave Alternans

A 64 year old man with a 20 year history of renal failure, and a history of an MI 12 years prior to admission, presented with a new anterior myocardial infarction. His LVEF was 40% and he had NYHA class II heart failure.

Patient had a TWA test 3 weeks after his MI which was positive. Nine months later he died suddenly.

Syncope & Family History of SCD



Heart Rate

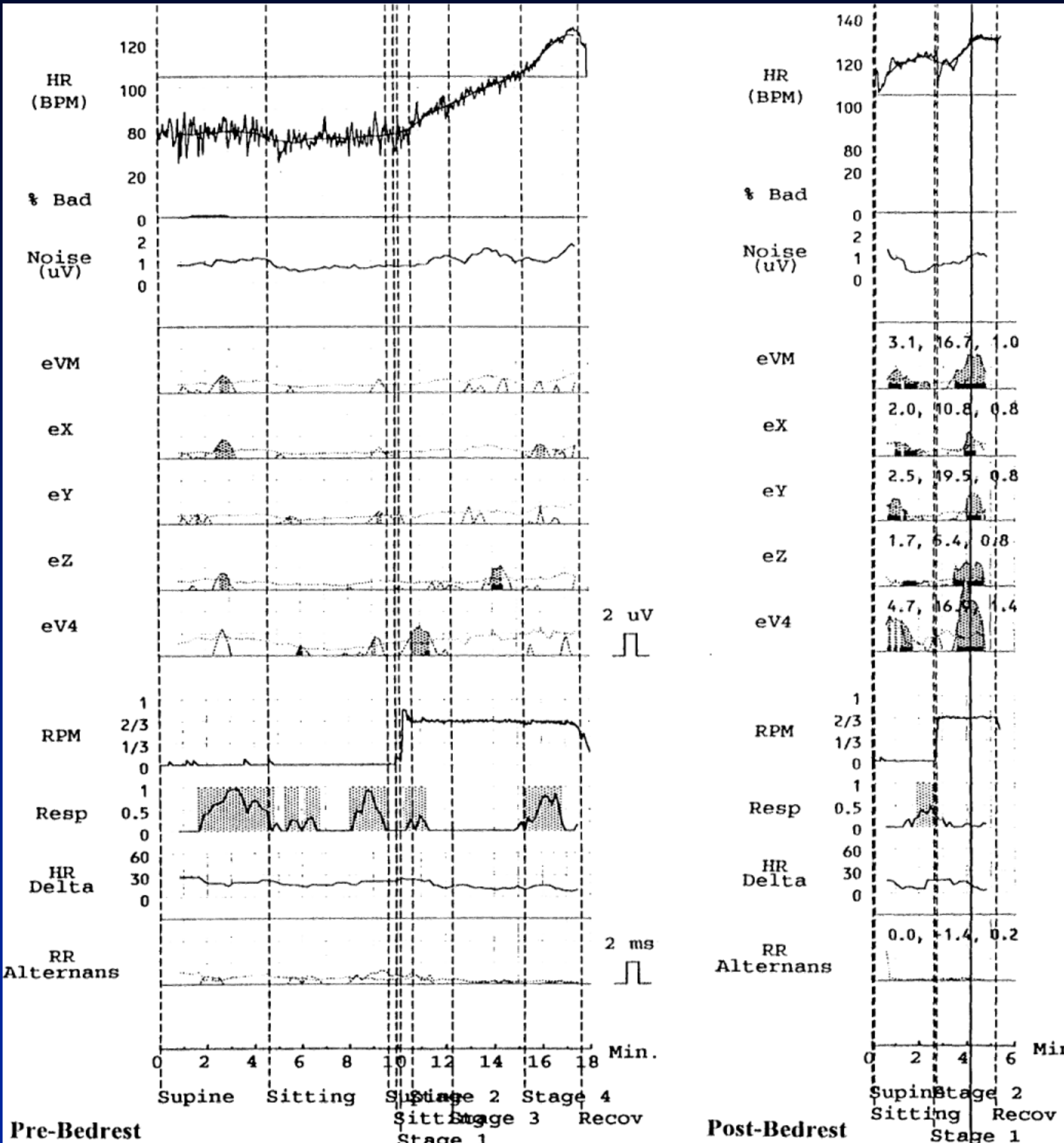
T-Wave Alternans

A 25-year-old male was evaluated for abrupt loss of consciousness. A family history of sudden death prompted the need for further evaluation. His LVEF was normal.

T-wave alternans testing was negative. At fifteen months follow-up, the patient had no tachyarrhythmic events.

Conclusions

- T-wave alternans appears to be a sensitive and specific marker of susceptibility to ventricular arrhythmias and sudden death in a wide variety of patient populations.
- T-wave alternans can be reliably measured during exercise stress with commercially available equipment.
- Event rate among T-wave alternans negative patients is extremely low.
- T-wave alternans can be used to identify patients requiring further diagnostic testing and treatment, thus increasing the effectiveness of treatment and reducing its cost.



Effect of Bed Rest on T Wave Alternans

Effect of T Wave Alternans

- Three of 11 subjects developed T wave alternans post bed rest. T wave alternans resolved over the next 2-3 days
- The onset heart for the development of T-wave alternans was above the standard cut-off (110 bpm) for clinical significance.
- Bed rest appears to affect cardiac repolarization processes.

Conclusions

- The cardiovascular system appears to adapt well to conditions of space flight, but loses its ability to cope with gravitational forces following landing.
- Space flight may adversely affect cardiac electrical stability and may lead to a reduction in cardiac mass.
- Further work is required to define the cardiovascular risks of space flight, understand mechanisms and develop appropriate countermeasures.
- Cardiovascular technologies developed for the space program have had spin-off benefits for civilian medicine.