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

Venous Resistance
- Venous Compliance
  - α-Sympathetic Input
  - Muscle Mass/Tone
- Venous Resistance
- Heart
  - Inotropy
  - HR Baroreflex
  - Parasympathetic Input
  - β–Sympathetic Input
  - Arrhythmias
  - Cardiac Atrophy
  - Angiotensin
- Intravascular Volume
  - Salt and Water Intake
  - AVP
  - ANP
  - Mineralocorticoids
- Arterial Compliance
- Microvascular Resistance
  - Resistance Baroreflex
  - Vasoreactivity
  - α–Sympathetic Input
  - AVP
  - Renin-Angiotensin System
  - Nitric Oxide
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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Natalie Sheynberg, M.D.
Gordon Williams, M.D.

Disciplines: Cardiology, Endocrinology, Space Medicine

Primary Source of Funding: National Space Biomedical Research Institute

GCRC Site Visit
# Experiment Protocol

<table>
<thead>
<tr>
<th>2 Days</th>
<th>16 Days</th>
<th>3 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive CV &amp; Endocrine Testing</td>
<td>4º HDT Bed rest</td>
<td>Extensive CV &amp; Endocrine Testing</td>
</tr>
</tbody>
</table>

**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

ABP (Finapres)

ECG

ILV (Respitrace)

Amplifier → A/D → System Identification

System Identification Results
CSI
Effect of Autonomic Blockade
CSI
Effect of Autonomic Neuropathy
HR Baroreflex Sensitivity

In(Max Amplitude) of APB→HRT

- Supine
- Standing

Phase:
- Pre-Bedrest
- End-Bedrest
- Post-Bedrest

BPM/mmHg/sec:
- -1.80
- -1.60
- -1.40
- -1.20
- -1.00
- -0.80
- -0.60
- -0.40
- -0.20
- 0.00
Effect of Midodrine

Pre-Bedrest

Post w/o Midodrine

Post with Midodrine

HR in beats/min

BP in mmHg

HR in beats/min

BP in mmHg

HR in beats/min

BP in mmHg
Kaplan-Meier Syncope-Free Survival

Control

Midodrine

P = 0.021

Time (Minutes)

Syncope-Free Survival

0 40 80 120 160

0 10 20 30 40 50 60 70 80 90 100
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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Population Size (millions)</th>
<th>SCD Percent / Year (percent)</th>
<th>Total SCD / Year (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Coronary Risk</td>
<td>20</td>
<td>30</td>
<td>200</td>
</tr>
<tr>
<td>Post M I</td>
<td>10</td>
<td>15</td>
<td>150</td>
</tr>
<tr>
<td>Heart Failure/EF &lt; 35%</td>
<td>5</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Syncope/Heart Disease</td>
<td>1</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Previous VF/VT</td>
<td>0.5</td>
<td>1.5</td>
<td>15</td>
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</table>

Adapted from Myerburg
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 admission. 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.
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.
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


2. Lewis T: Notes upon alternation of the heart. Quart J Med 1910; 4:141-144.


(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

ECG

TIME SERIES

SPECTRUM

FFT

128 Beats

T Wave Level (µV)

Beat Number

Spectrum (µV²)

Frequency (Cycles/Beat)
T-Wave Alternans Measurement: Spectral Method

ECG

128 Beats

FFT

Avg

Spectrum (µV²)

Frequency (Cycles/Beat)

Resp

Pedaling

Alternans

Frequency (Cycles/Beat)
T-Wave Alternans Measurement: Spectral Measures

Alternans Voltage ($V_{alt}$)

$V_{alt} = \left(\text{Alternans Power}\right)^{\frac{1}{2}}$

Alternans Ratio ($k$)

$k = \frac{\text{Alternans Power}}{\text{Noise Std. Dev.}}$
Heart Rate Dependence of TWA

ALTERNANS (µV)

VT PATIENT

CONTROL

HEART RATE (BPM)

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) $57 \pm 16$
- 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%

Electrical Alternans Versus Electrophysiologic Testing

LVEF (%)

MI (%)

ST Alternans Ratio

T Alternans Ratio

SHD: Structural Heart Disease

MGH / MIT Results
Arrhythmia Free Survival

Alternans Test

EP Study

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%

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%

Multi-Center Regulatory Study
Prediction of VT/VF, ICD Firing and Total Mortality

Alternans Test

RR = 13.9
P < 0.001

EP Study

RR = 4.7
P = 0.001

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%

Frankfurt CHF Study Results

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

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 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

Comparison to Other Risk Markers

Prediction of Arrhythmia-Free Survival

Armoundas et al, 1998
Hohnloser et al, 1998
Gold et al, 1999
Klingenheben et al, 2000

NSVT
HRV
SAECG
TWA

* p < 0.01
# Event Rates Among TWA+ and EP+ Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Follow-Up (months)</th>
<th>TWA+</th>
<th>EP+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenbaum, et al NEJM, 1994</td>
<td>EP</td>
<td>20</td>
<td>81%</td>
<td>~81%</td>
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<tr>
<td>Ikeda, et al JACC, 2000</td>
<td>Post MI</td>
<td>12</td>
<td>28%</td>
<td></td>
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<tr>
<td>Gold MR, et al FDA, 1999 JACC, in press</td>
<td>Known or Suspected Ventricular Arrhythmia (EP)</td>
<td>13</td>
<td>26%</td>
<td>25%</td>
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<tr>
<td>Bloomfield, et al Circ, 1999 (abs)</td>
<td>Syncope (EP)</td>
<td>13</td>
<td>19%</td>
<td>21%</td>
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<tr>
<td>Klinghenheben, et al The Lancet, 2000</td>
<td>CHF</td>
<td>18</td>
<td>21%</td>
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<tr>
<td>Klinghenheben, et al PACE, 1999 (abs)</td>
<td>DCM</td>
<td>6</td>
<td>21%</td>
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<tr>
<td>Buxton, et al NEJM, 2000</td>
<td>Prior MI, EF ≤ 0.40, NSVT</td>
<td>24</td>
<td></td>
<td>18%</td>
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# Event Rates Among TWA- and EP-Patients

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<th>TWA-</th>
<th>EP-</th>
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<tr>
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<td>20</td>
<td>6%</td>
<td>~6%</td>
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<tr>
<td>Ikeda, et al JACC, 2000</td>
<td>Post MI</td>
<td>12</td>
<td>2%</td>
<td></td>
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<tr>
<td>Gold MR, et al FDA, 1999</td>
<td>EP</td>
<td>13</td>
<td>2%</td>
<td>5%</td>
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<tr>
<td>Gold MR, et al FDA, 1999</td>
<td>Known or Suspected Ventricular Arrhythmia (EP)</td>
<td>13</td>
<td>3%</td>
<td>8%</td>
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<tr>
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<td>Syncope (EP)</td>
<td>13</td>
<td>3%</td>
<td>6%</td>
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<tr>
<td>Klingeneben, et al The Lancet, 2000</td>
<td>CHF</td>
<td>18</td>
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<td>DCM</td>
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<td>0%</td>
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</tr>
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<td>Prior MI, EF ≤ 0.40, NSVT</td>
<td>24</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>
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
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

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.
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.
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.
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.