Neural and Emotional triggers in Acute coronary syndrome
Neural and Emotional triggers in Acute coronary syndrome

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Scheme

• ACS- A brief
• Vulnerable plaque
• Risk factor vs triggers
• Epidemiological data
• Clinical evidence
• Impact of various emotions
• Physiological basis of neural link
• Pacifying triggers
• Prevention
Acute coronary syndrome

- Acute MI / STEMI
- Unstable angina/NSTEMI
- Sudden cardiac death
Global burden of coronary heart disease

Coronary heart disease burden is projected to rise from around 47 million DALYs globally in 1990 to 82 million DALYs in 2020.

Healthy years of life lost to coronary heart disease

DALYs lost per 100,000 population, age-standardized estimates for 2002

More than 60% of the global burden of coronary heart disease occurs in developing countries.

Disease burden in men
Percentage of DALYs lost due to top ten diseases in men aged 15 years and above

Disease burden in women
Percentage of DALYs lost due to top ten diseases in women aged 15 years and above

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Global Causes of All Deaths

- Communicable, maternal, perinatal: 27%
- Cardiovascular Diseases: 31%
- Injuries: 9%
- Cancer: 13%
- Respiratory Diseases: 8%
- Other NCDs: 10%
- Diabetes: 2%

Legend: Non-Communicable Diseases (NCDs) Other Causes of Death

Source: DATA: World Health Organization

IMAGE: www.HeartNewslinks.com
Acute coronary occlusion
Primary PCI: The new age modality
ACS–Outcome

- Greatly improved
- Still Prohibitive
- 20% out of hospital
- 7 % in CCU
- 10 % 1 year

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What is the culprit?
1° & Messenger Inflamm. Cyto/Chemokines

Cellular Adhesion Molecules

Plaque Destabilization

Plaque Rupture

Foam Cell 
Fatty Streak 
Intermediate Lesions 
Atheroma 
Fibrous Plaque 
Complicated Lesion/Rupture

IL-1 
TNF-α 
IL-18 
MCP-1

IL-6*
sICAM

sVCAM

sSelectins

IL-18*

oxLDL*

Lp-PLA₂*

GPx-1*

MPO*

MMPs *

MCP-1*

PIGF*

PAPP-A*

sCD40L*

Acute Phase Reactants

CRP*, sPLA₂*, SAA, Fibrinogen, WBCC

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Lipid core / Fibrous Cap / plaque stress / fatigue

Eccentric soft gruel

Critical points at cap shoulders
Ischemic Discomfort
Acute Coronary Syndrome

Presentation

Working Dx

ECG

Cardiac Biomarker

Final Dx

No ST Elevation

Non-ST ACS

ST Elevation

UA

Unstable Angina

NSTEMI

Myocardial Infarction

NQMI

Qw MI

UA

NSTEMI

Myocardial Infarction
MMP central role  plaque vulnerability?

20 MMPs identified collectively called matrixins, are proteinases
MMP 8 culprit
Degrades fibrillor collagen

TIMP

Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors
Trapping the killer MMP with TIMP 2
Risk factors vs Triggers
Framingham Risk Calculator

- Age
- Gender
- Smoker
- Total cholesterol
- HDL-C
- Systolic BP
- HTN Rx

Calculates 10-year risk for CHD death or nonfatal MI

High risk: > 20%
Intermediate risk: 10-20%
Low risk: < 10%

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**Trigger**: An activity that produces short-term physiological changes that may lead directly to onset of acute CVD.

**Acute risk factor**: A short-term physiological change, such as a surge in arterial pressure or heart rate, an increase in coagulability, or vasoconstriction, that follows a trigger and may result in disease onset.

**Hazard period**: The time interval after trigger initiation associated with an increased risk of disease onset because of the trigger. The onset and offset times of the hazard period, which could also be designated a “vulnerable
“For every ACS to manifest a trigger . . . seems to be essential over and above the baseline chronic risk profile”
Types of triggers

Physical
Emotional
Neural
Systemic illness
Physical triggers – early evidence

Clustering of events
Diurnal variation
Physical exertion
Elevation of Stroke and MI Upon Awakening

Adapted from Elliot WJ. *Am J Hypertens.* 2001;14:291S-295S.
Figure 2. Changes in Blood Pressure (BP) and Heart Rate (HR) in a 24-Hour Period
EDITORIAL

Can we trigger an acute coronary syndrome?

R A Kloner


Emotional triggers in myocardial infarction: do they matter?

Donald Edmondson, Jonathan D. Newman, William Whang, and Karina W. Davidson*

Center for Behavioral Cardiovascular Health, Department of Medicine, Columbia University Medical Center, New York, NY, USA
Negative emotions

- Fear
- Anger
- Anxiety
- Depression

Where is the evidence coming from?

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Population-Based Analysis of the Effect of the Northridge Earthquake on Cardiac Death in Los Angeles County, California

Robert Adlerer, Jonathan Lean, W. Kenneth Poole, Rebeca Perel
J Am Coll Cardiol 1997;30(5):1174-1180
Figure 1:
Kaplan-Meier survival curve comparing probability of implantable cardioverter-defibrillator (ICD) discharges for termination of ventricular tachycardia or ventricular fibrillation (event at 9/11) for 30 days before and 30 days after September 11. A significantly greater proportion of patients experienced ICD discharges after the World Trade Center attack.

Figure 2:
The day-to-day incidence of ventricular tachyarrhythmias triggering implantable cardioverter-defibrillator therapy during an eight-month observation period, with a substantial increase in event rate in the 30-day period after September 11, 2001, followed by a return to baseline.
Increased Incidence of Life-Threatening Ventricular Arrhythmias in Implantable Defibrillator Patients After the World Trade Center Attack

Jonathan S. Steinberg, MD, FACC,*† Aysha Arshad, MBBS,* Marcin Kowalski, MD,* Atul Kukar, DO,* Valentin Suma, MD,* Margot Vloka, MD,*† Frederick Ehler, MD,*† Bengt Herweg, MD,*† Jacqueline Donnelly, BA,* Julie Philip, PA-C,* George Reed, PhD,*‡ Alan Rozanski, MD, FACC*

New York, New York; Ridgewood, New Jersey; and Worcester, Massachusetts
When Stocks Drop, Heart Attacks Rise

By ALAN FARNHAM - Jan. 7, 2014

A stock market slide can send you to the hospital. That's the finding of a new study by two U.C. San Diego finance professors who correlated 30 years of California hospital admission records with the ups and downs of the stock market.

"Worrying About the Stock Market: Evidence from Hospital Admissions," by professors Joseph Engelberg and Christopher Parsons, was recently presented at the annual meeting of the American Economic Association. The authors have submitted it for peer review to the Journal
National sports loss as a trigger
Cricket fan dies after World Cup rout

IANS, Patna  |  Updated: Mar 25, 2007 13:20 IST

A cricket fan in Bihar died of heart attack soon after India's shocking defeat to Sri Lanka in the World Cup while another was critical following cardiac arrest, reports said on Sunday.

Panna Lal Agrawal, a chemist in Bankebazaar in Gaya district, around 100 km from Patna, died Friday night after India lost to Sri Lanka. Agrawal was in his 50s.

Karun Kumar Pathak of the same district was admitted to hospital after a massive cardiac arrest following Team India's loss. Pathak, a
Plaque Destability

- Hemodynamic
- Hematological
- Cytokines
- Inflammation

Psycho social

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Scientific evidence
ONSET (Mittleman NEJM1993)

SHEEP (J Epidemiol Commun Health. 2005)

TRIMM (Willich NEJM 1993)
Figure 3. Possible triggers of acute MI. A possible trigger was reported by 412 (48.5%) of 849 patients from the Multicenter Investigation of Limitation of Infarct Size (MILIS). A total of 109 patients (13%) reported 2 or more possible triggers. Adapted from Tofler et al\textsuperscript{27} with permission from Elsevier. Copyright 1990.
Physical exertion as trigger

**Graph:**

- **Y-axis:** Relative Risk of Exertion-Induced MI
- **X-axis:** Usual Activity Level
  - Very low
  - Low
  - Moderate
  - High

- **Legend:**
  - The bar chart shows a higher relative risk of exertion-induced MI for very low activity levels compared to low, moderate, and high activity levels.
Sexual activity as trigger

ONSET/SHEEP data specific analysis (>2.5-3 fold)
There is a casual association
Low absolute risk
Different from Gen population /Post MI

Anger as Trigger

Circulation

Triggering of Acute Myocardial Infarction Onset by Episodes of Anger

Murray A. Mittleman, MDCM, DrPH; Malcolm Maclure, ScD; Jane B. Sherwood, Determinants of Myocardial Infarction Onset Study Investigators

1995;92:1720–1725
Case-crossover Study Design

Usual Frequency of Exposure During Past Year

Comparison 1

Exposure in Control Period
One Day Before

Comparison 2

Exposure in Hazard Period
Immediately Before MI

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Timing of anger and the event

Relative Risk of Onset of MI

Time of Anger (hours before onset)

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Our experience

Estimation of Subjective Stress in Acute Myocardial Infarction

Chockalingam A, Venkatesan S, Dorairajan S, Moorthy C, Chockalingam V, Subramaniam T
Department of Cardiology, Madras Medical College and Research Institute, Chennai - 600 003

53 % had life stress events
Emotional triggers: Summary

Overwhelming epidemiological data
Individual cases reports
Community statistics
Anger and acute life stress dominated
Dual risk for emotions: Acts both as trigger / Risk factor
Physiological basis of the Neuro–emotional cardiac link
Anger, emotion, and arrhythmias: from brain to heart

Peter Taggart¹*, Mark R. Boyett², Sunil Jit R. J. Logantha² and Pier D. Lambiase³

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² Cardiovascular Medicine, University of Manchester, Manchester, UK
³ Department of Cardiology, University College London Hospitals, London, UK

Central sympathetic network

Cingulate gyrus
Frontal
Temporal
Parietal
Sympathetic pathways to and in the heart are shown here. All four chambers are richly endowed with sympathetic nerves, with heavy concentrations in the regions of the SA and SV nodes. The atria appear to be more densely innervated than the ventricles.
Neurobiology of stress

Neuro- endocrine activation
Immuno inflammatory vascular pathway

5 fold increase in cardiac events

Ref 1. Frassure Smith (Circulation 1995)
2. Van malle 2004 psychosomatic medicine Meta analysis
A broken heart is not just folklore

A new study examines 19 patients who suffered cardiac problems following sudden emotional stress. The study offers a possible explanation.

1. Grief or fear is experienced ...

2. ... stimulating the adrenal glands and nerves to produce stress hormone including adrenaline ...

3. ... that can sharply lower the heart’s pumping ability

4. The reduced pumping causes chest pain and other symptoms similar to a heart attack

SOURCE: New England Journal of Medicine
Catecholamine toxicity
Emotional and physical stress

- Excitation of limbic system, hypothalamus
- Excitation of medullary autonomic center
- Excitation of presynaptic sympathetic neuron
- Excitation of postsynaptic sympathetic neuron

Increased activities in neuronal cells and cardiac cells

Reduction of estrogen following menopause

Decreased NO production  Down-regulation of HSP70 and ANP

β-Receptor

NE  Epi

α-Receptor

Increase of blood pressure and afterload

Contraction of arteries  Disturbance of coronary circulation

Oxidative stress

Hypococontraction of LV apex

Increase of oxygen demand  Catecholamine toxicity

Mechanical wall stress

Hypercontraction and obstruction of LV outflow
Looking beyond catecholamine
Orexnergic system
(hypocretin receptor)

• Cortical - Hypothalamic arousal system
• Stimulation causes the elevation of BP
• High levels are associated with hyper arousal / Stress
Hyper-arousal is a trigger
Acute trigger

Physiological responses
- Haemodynamic response
- Autonomic dysfunction
- Neuroendocrine activation
- Inflammatory response
- Prothrombotic response

Pathophysiological effects
- Myocardial ischaemia
- Cardiac dysrhythmia
- Plaque disruption
- Thrombus formation

Clinical events
- Myocardial infarction
- Unstable angina
- Ventricular Tachycardia/fibrillation
Stress and hematological effects

Pro-coagulant hemostatic responses
Increased blood viscosity
Fibrinogen concentration

*Increased platelet adhesion*
Stress and hematological effects
Serotonin : Brain–Platelet interaction

5HT receptor density increased
5HT transporter reduced both in brain and platelet
Intracellular calcium increase
Platelet factor 4 and B Thromboglobulin

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Neuro electrical trigger
Clinical evidence for Neuro cardiac link

Stroke
Epilepsy
Stress cardiomyopathy
ECG in stroke
Holter recording during seizures
Sudden cardiac deaths during seizures: The mystery of ictal asystole and VF

Seizure induced ventricular fibrillation: A case of near-SUDEP Monica Ferlisi, Ruggero Tomei, Monica Carletti. Seizure Volume 22, Issue 3, April 2013, Pages 249–251

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Mechanism of primary VF
Is the heart a neurological end organ?

Paraventricular nucleus
Triggers VF in animals
Para sympathetic vs sympathetic. Right vs left

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Neural sprouting
Neural sprouting – S 100 positive fibrotic myocardium
Evidence for benefits with Neuronal blockade

Cervical sympathectomy
Beta blockers
Post transplant hearts

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Beta blockers

Key role Entire spectrum of CAD

Backed by mega trials, without dispute
Learning from de-nerved heart
The concept of emotional stress testing
Can we screen for the trigger prone?
Lessons from a lost President

A charming dreamer, deep love for the nation... gave his life Unknown Trigger?
Emotional stress testing

ST depression
Wall motion defect

Newer protocols are defined
PET imaging of emotions
In Search of Coronary-Prone Behavior
Beyond Type A

Edited by
Aron W. Siegman
Theodore M. Dembroski

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Catecholamine Imaging

**NYHA I**

H/M: 2.34, WR: 15%

**NYHA III**

H/M: 1.45, WR: 39%

**Washout Rate** =\[
\frac{\text{Early (H} - \text{M)} - \text{Delayed (H} - \text{M)}}{\text{Early (H} - \text{M)}} \times 100
\]

*Reduced myocardial stores, Rapid washout, and spill over in CHF*
Treating Depression and prevention of cardiac events

• SAD - HEART
• CREATE
• MIND IT

Markovitx Mathews psychosomatic medicine, 1991
Musselman, Manatunga Am J of psychiatry, 1997
Positive emotions: Protection

- Prayer
- Social support
- Yoga
- Meditation
- Music

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Passivating triggers

Avoiding extreme exertion
Improving emotional intelligence
Anger management
Drugs – Antidepressant
Public health measure (Air pollution / disaster response / Aiming for social peace)
Concluding messages

• Strong neuro cardiac link in ACS exist.
• Triggers are vital
• Baseline risk factor is the key
• Triggers per-se for fatality seems rare.
• Standard medical treatment is crucial
Can we eliminate these triggers Completely?

Emotions Integral part of life

Only a fraction transform to clinical events

What is the missing link?
Knowledge will evolve . . .

- Time ?
- Metaphysics ?
- Heisenberg ?
“Meanwhile . . . It’s highly likely a cool mind can definitely prevail over the heart”