

# Neural and Emotional triggers in Acute coronary syndrome



# Neural and Emotional triggers in Acute coronary syndrome



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**Madras medical college , Chennai**

# 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

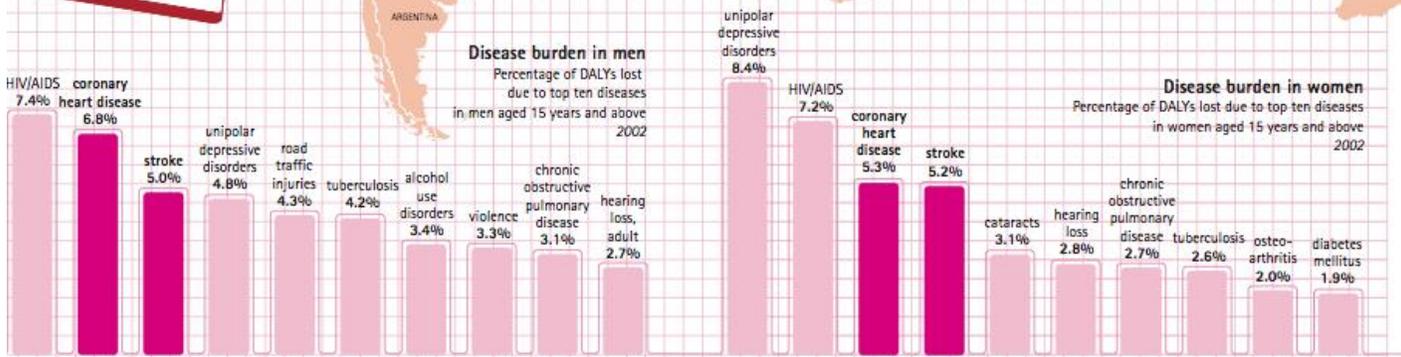
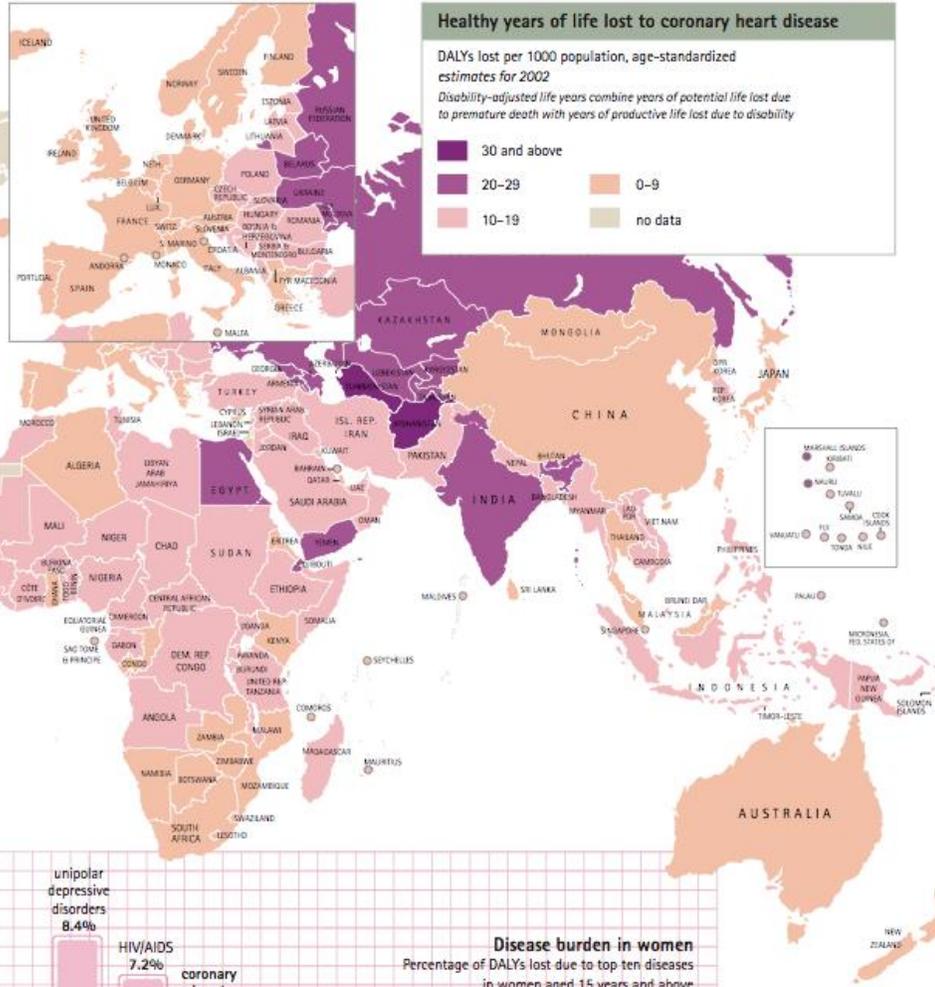
- **Acute MI /STEMI**
- **Unstable angina/NSTEMI**
- **Sudden cardiac death**

# Global burden of coronary heart disease

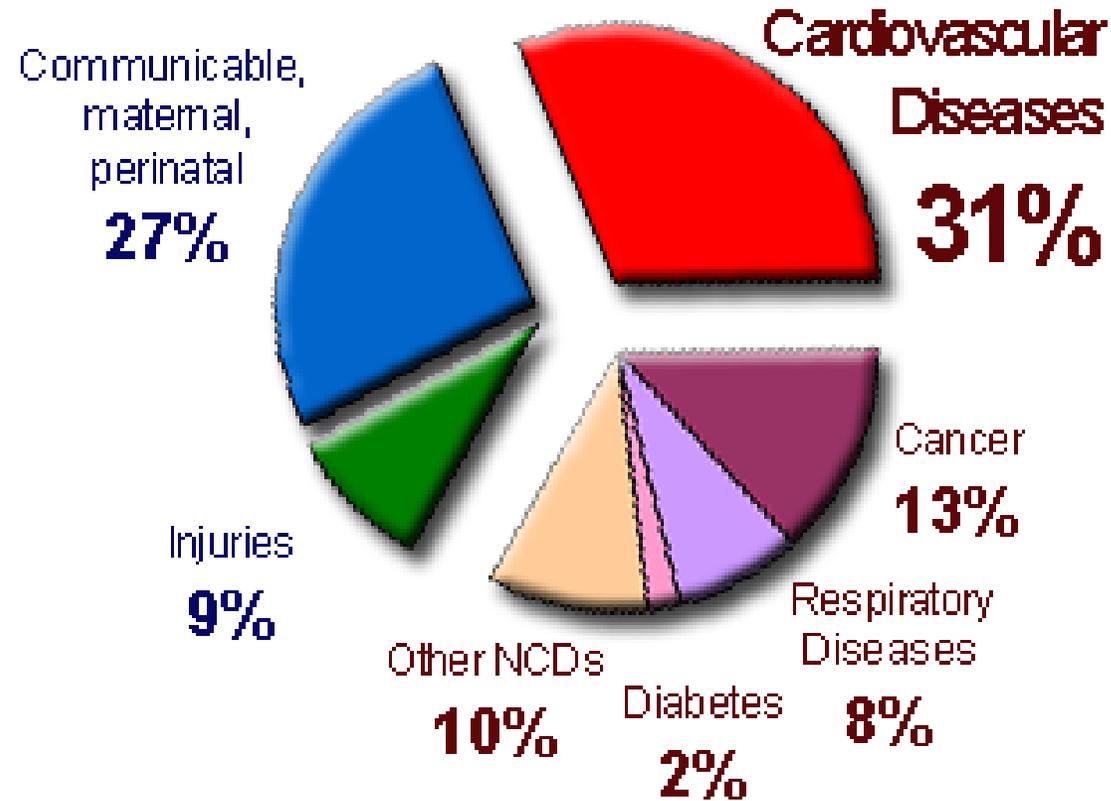


Coronary heart disease burden is projected to rise from around 47 million DALYs globally in 1990 to 82 million DALYs in 2020.

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



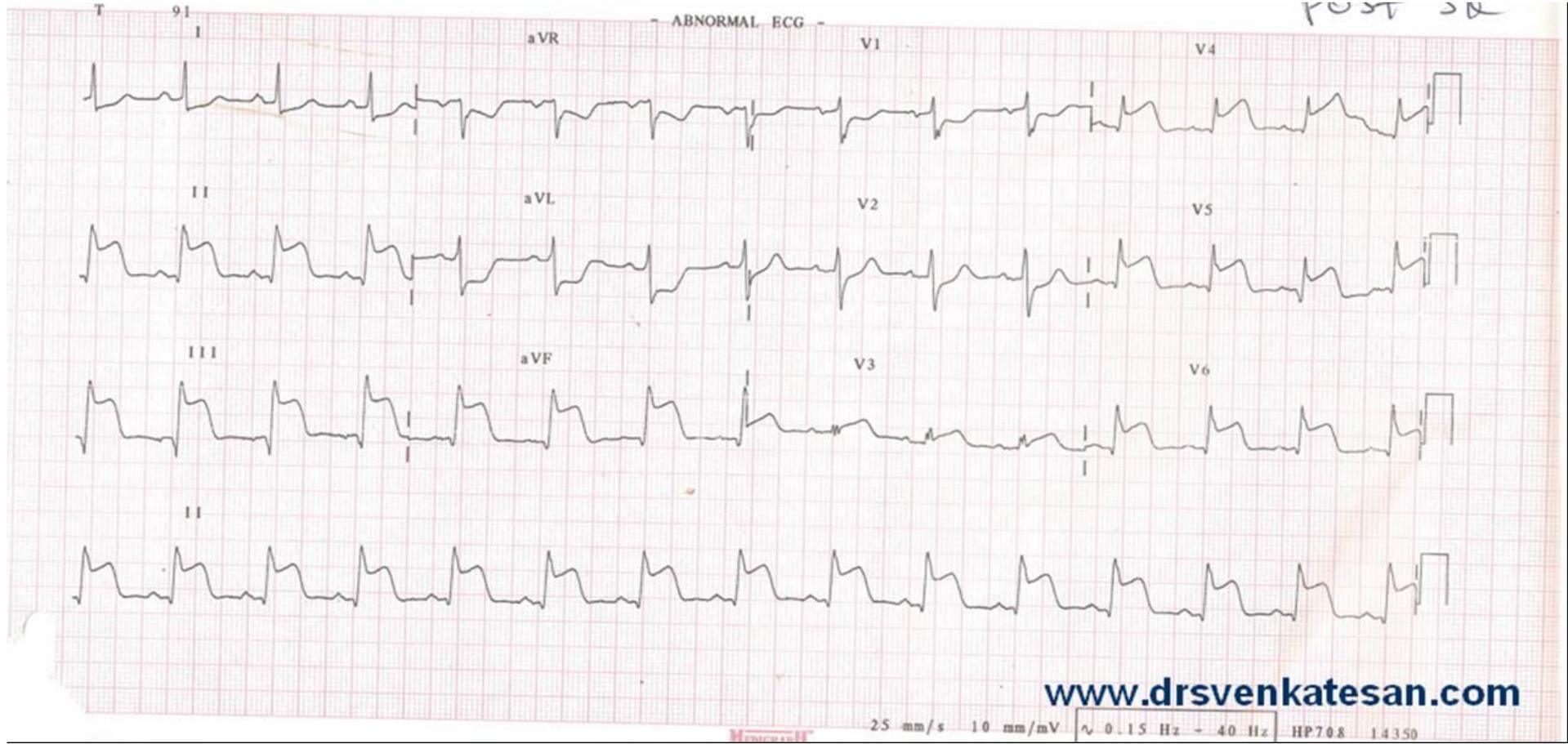
# Global Causes of All Deaths



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

Source: DATA: World Health Organization  
Global Atlas on cardiovascular disease prevention  
and control Geneva 2011

IMAGE: [www.HeartNewsLinks.com](http://www.HeartNewsLinks.com)



# Acute coronary occlusion





**TNKase®** SINGLE-BOLUS  
**Tenecteplase**





# Primary PCI : The new age modality

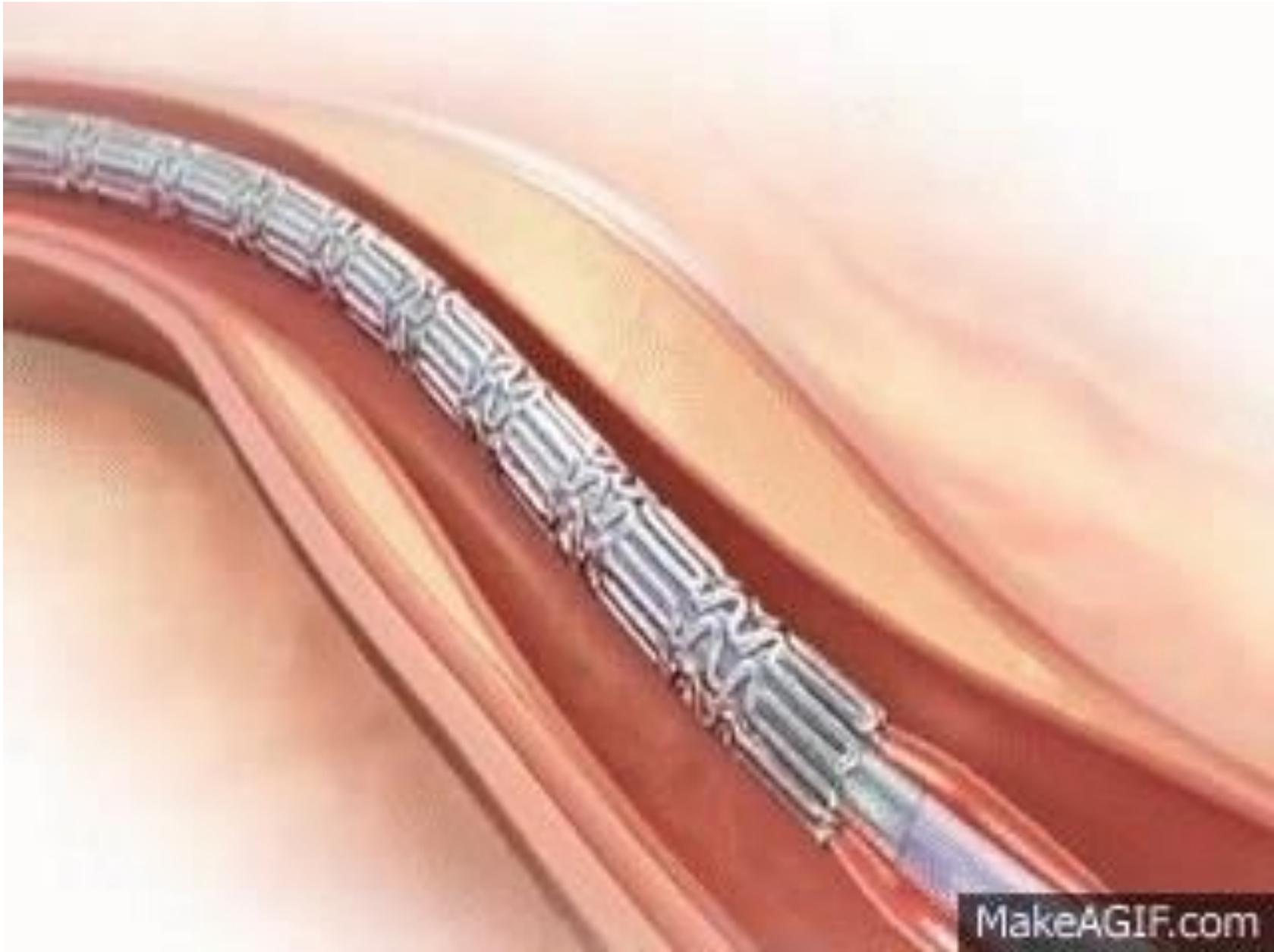
[www.drsvenkatesan.com](http://www.drsvenkatesan.com)

Im: 1/150  
Sec: 40

SHARADHANI | 57/M (PSCA)  
A NO 1877 | IPNO122859  
1-01-1957 M  
Hospital  
I.0.8051852

WL: 333 Wk: 247 (T)  
KAC: 40 CR: 40

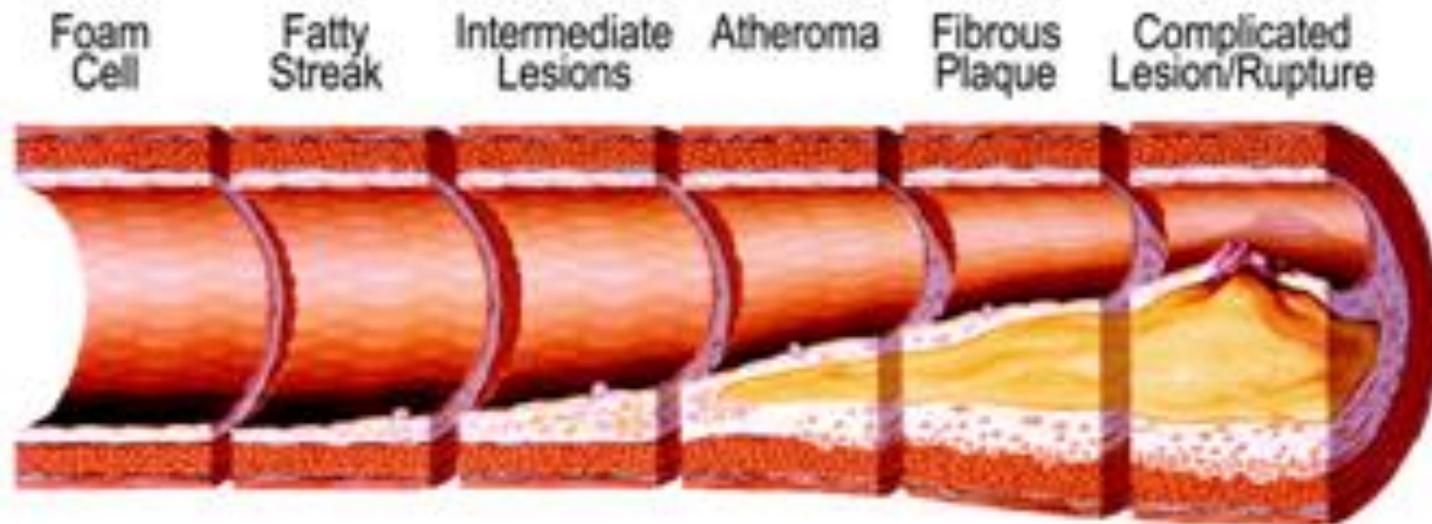
2014-01-14 10:51:04



# ACS–Outcome

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

What is the culprit ?

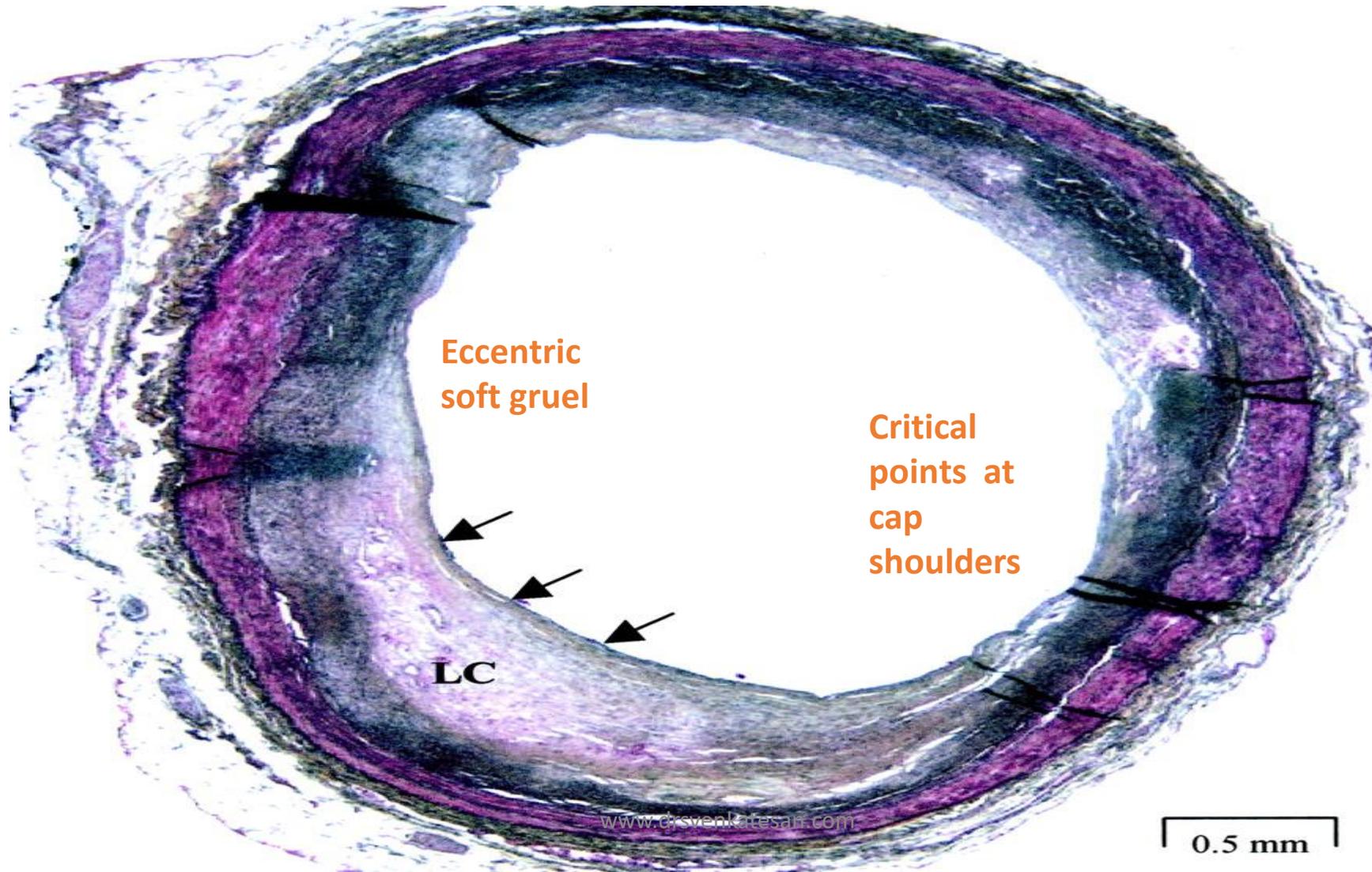


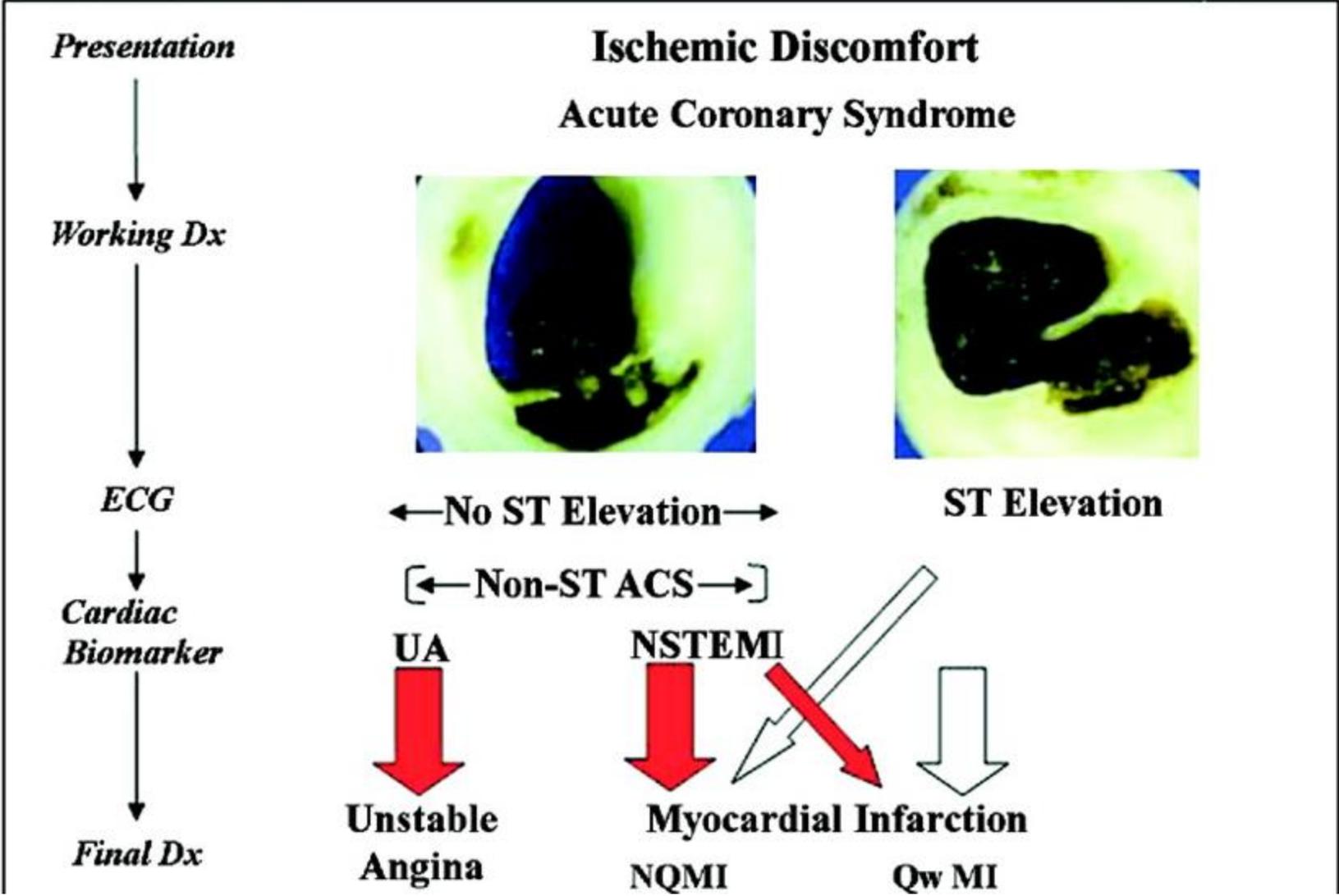
1° & Messenger Inflamm. Cyto/Chemokines		Cellular Adhesion Molecules	Plaque Destabilization		Plaque Rupture
IL-1	IL-6*	sICAM	IL-18*	MPO*	PAPP-A*
TNF- $\alpha$	IL-18*	sVCAM	oxLDL*	MMPs *	sCD40L*
	MCP-1*	sSelectins	Lp-PLA <sub>2</sub> *	MCP-1*	
			GPx-1*	PIGF*	



Acute Phase Reactants  
 CRP\*, sPLA<sub>2</sub>\*, SAA, Fibrinogen, WBCC

# Lipid core / Fibrous Cap/ plaque stress/ fatigue





# MMP central role plaque vulnerability ?

20 MMPs identified

collectively called matrixins, are proteinases

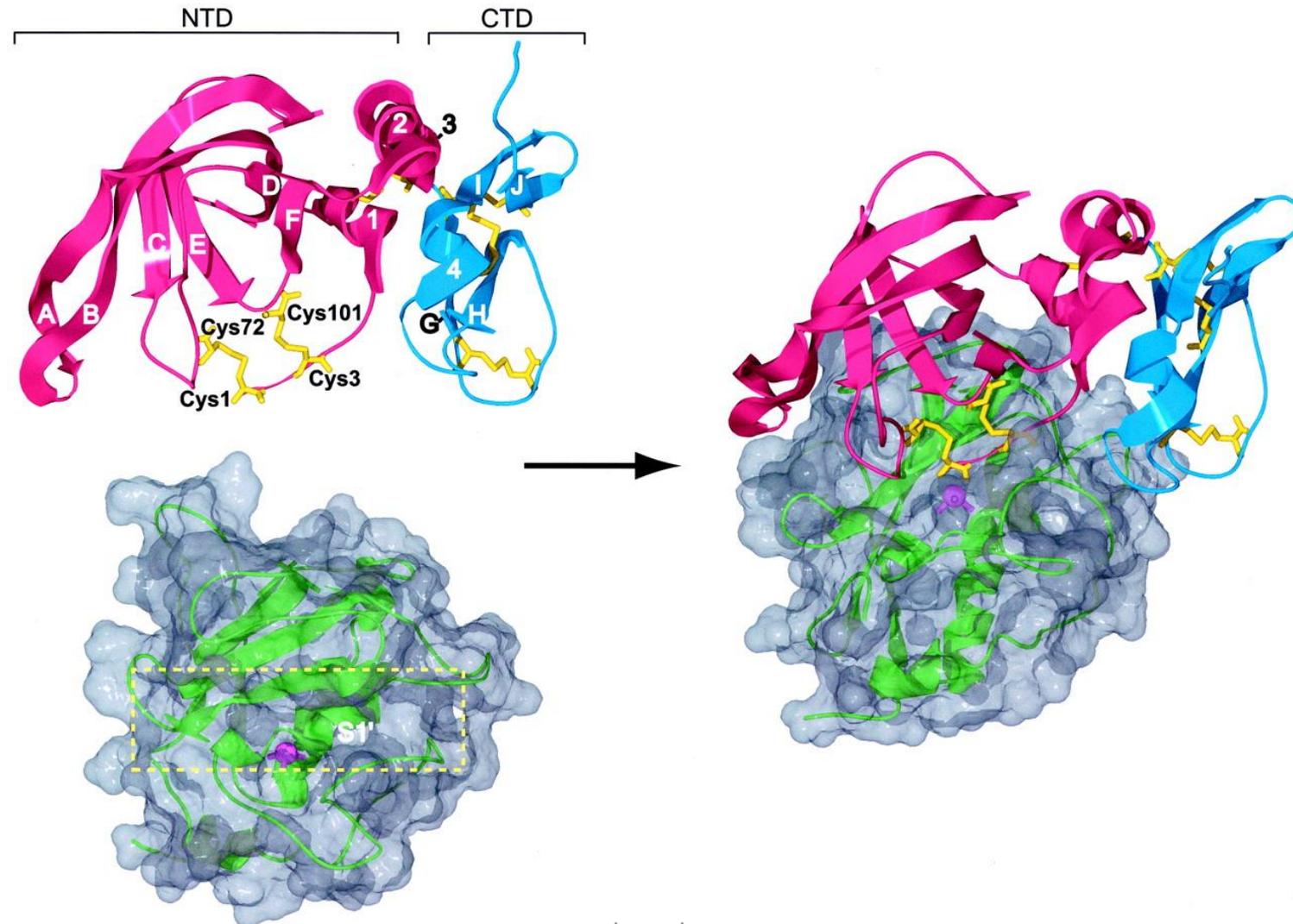
MMP 8 culprit

Degrades fibrillar collagen

## TIMP

Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors

# Trapping the killer MMP with TIMP 2



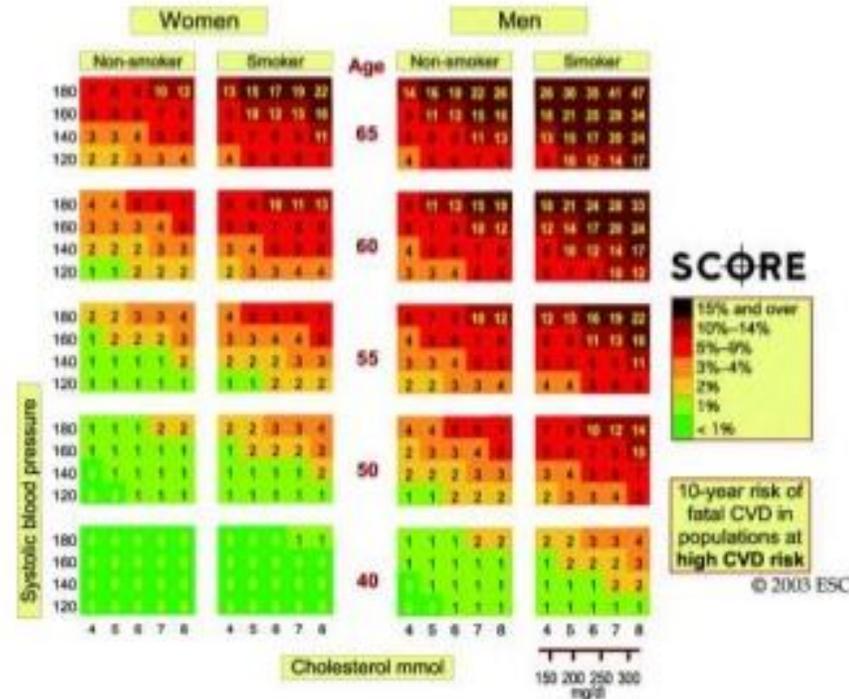
# **Risk factors vs Triggers**

# 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%

**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**

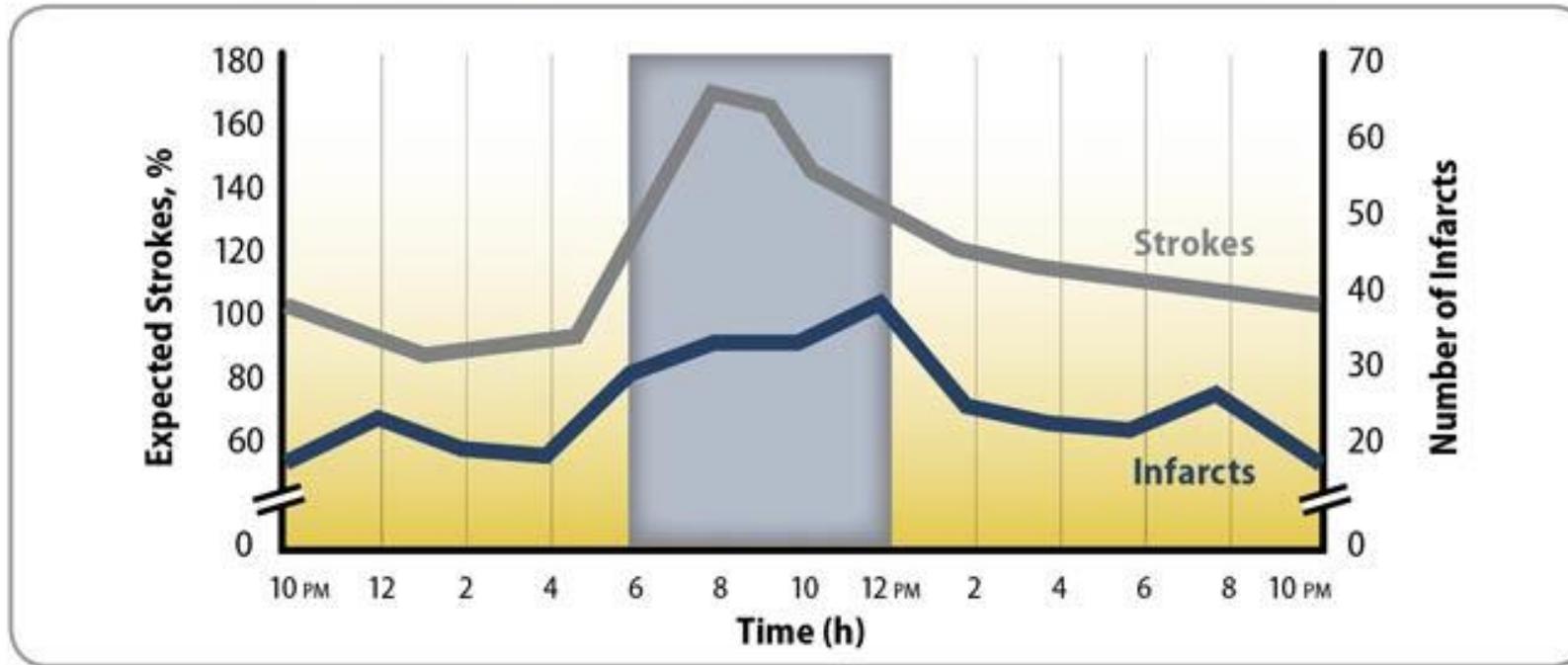
# Physical triggers –early evidence

Clustering of events

Diurnal variation

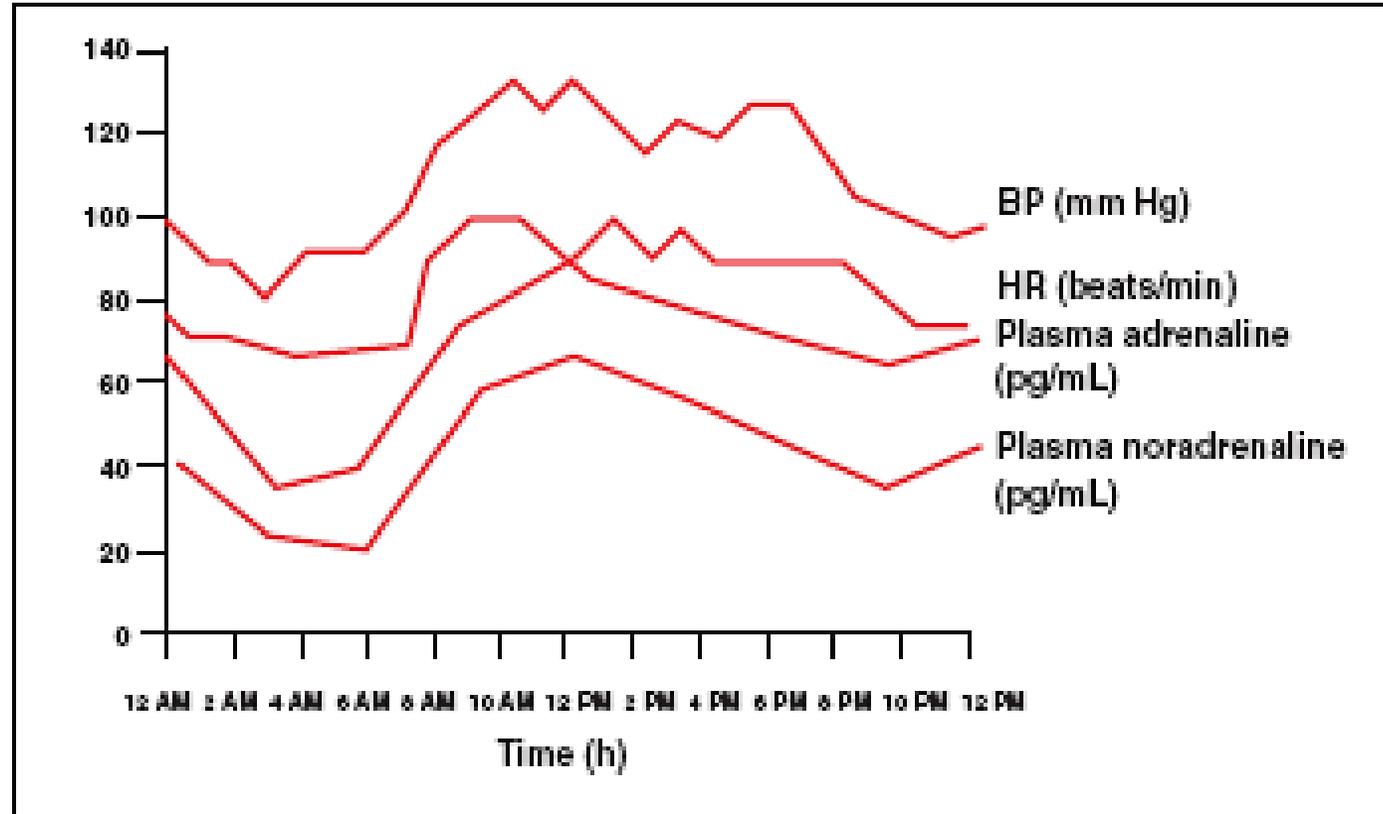
Physical exertion

## Elevation of Stroke and MI Upon Awakening<sup>2</sup>



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



Heart 2006;92:1009–1010. doi: 10.1136/hrt.2005.086652



European Heart Journal (2013) 34, 300–306  
doi:10.1093/eurheartj/ehs398

REVIEW

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

www.drsvenkatesan.com

# Negative emotions

- **Fear**
- **Anger**
- **Anxiety**
- **Depression**



**Where is the evidence coming from?**

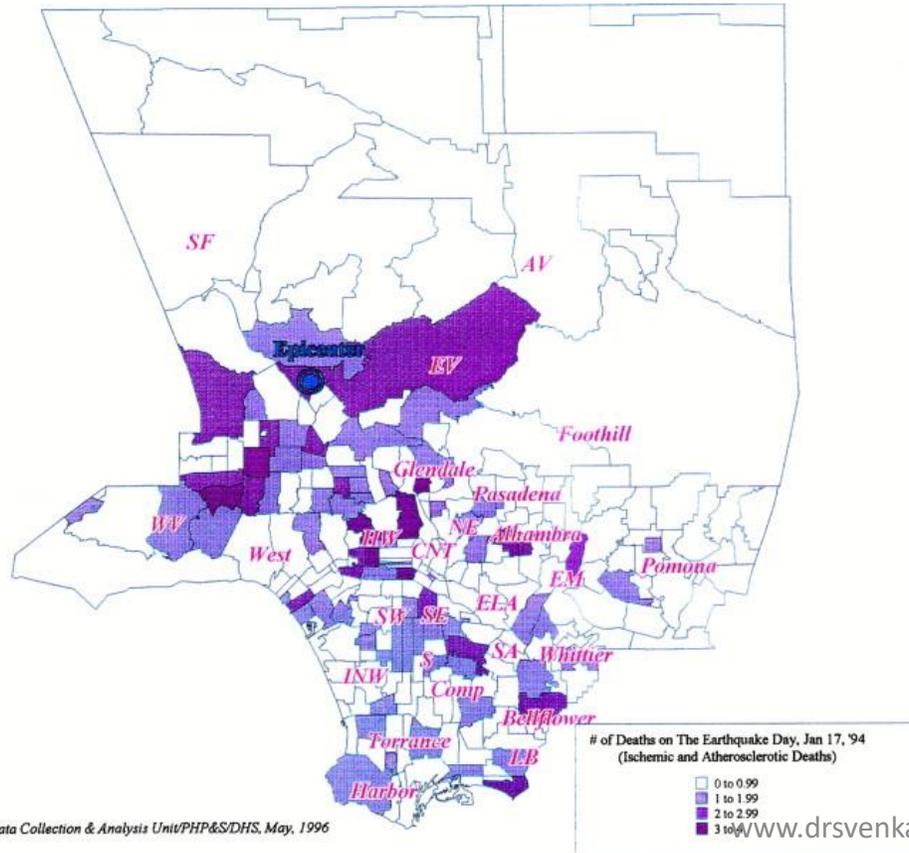


Clinical Studies: Cardiovascular Triggers | November 1997

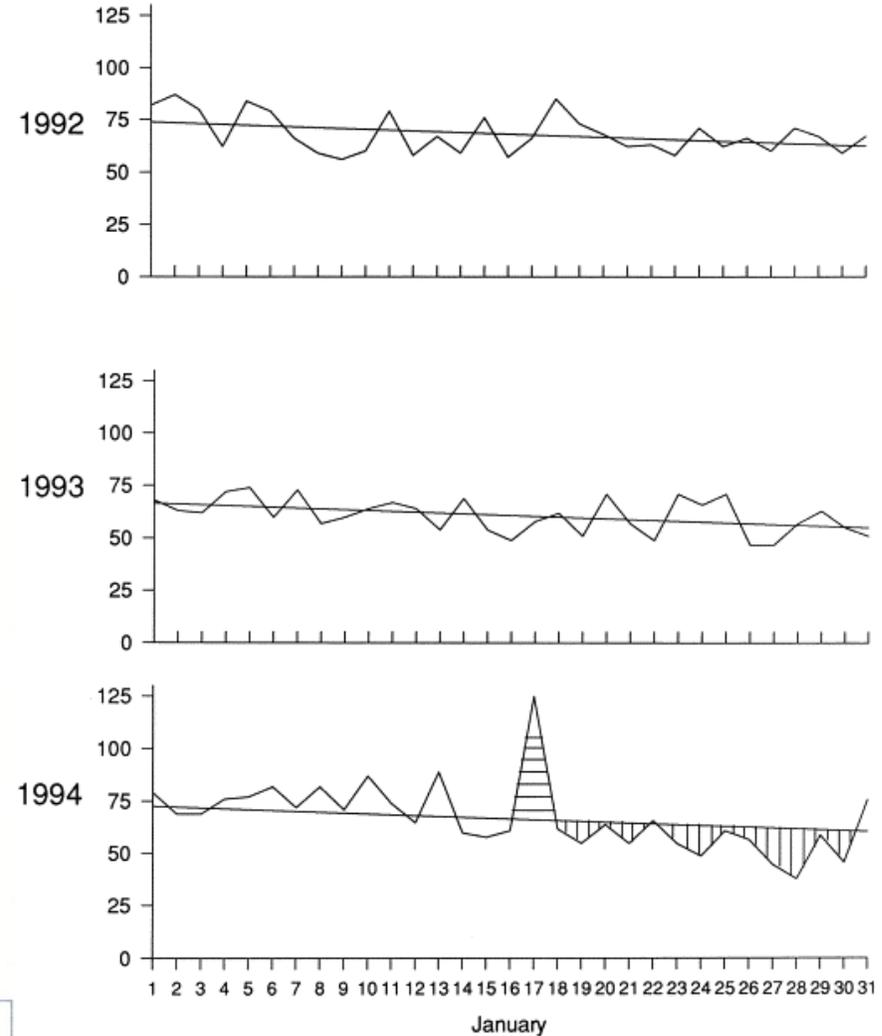
## Population-Based Analysis of the Effect of the Northridge Earthquake on Cardiac Death in Los Angeles County, California

Robert A Kloner Jonathan Leor W.Kenneth Poole Rebecca Perritt,

*J Am Coll Cardiol.* 1997;30(5):1174-1180



Data Collection & Analysis Unit/PHP&S/DHS, May, 1996



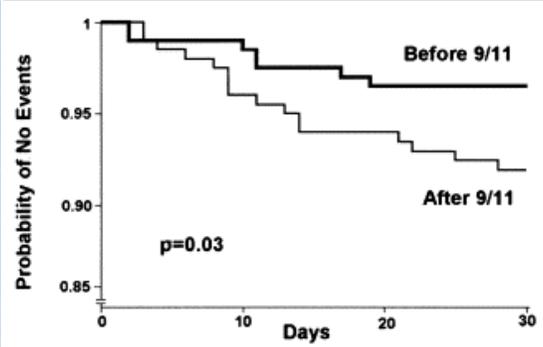


Figure 1. Kaplan-Meier survival curve comparing probability of implantable cardioverter-defibrillator (ICD) discharges for termination of ventricular tachycardia or ventricular fibrillation (**vertical axis**) for 30 days before and 30 days after September 11. A significantly greater proportion of patients experienced ICD discharges after the World Trade Center attack.

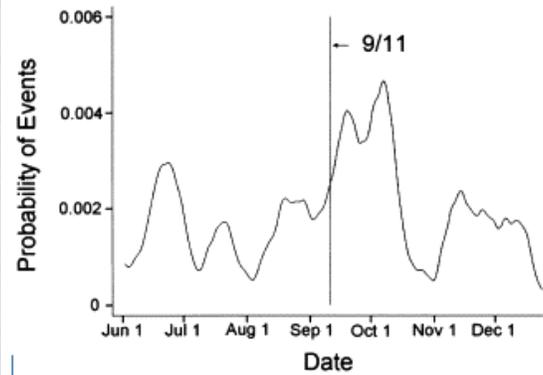
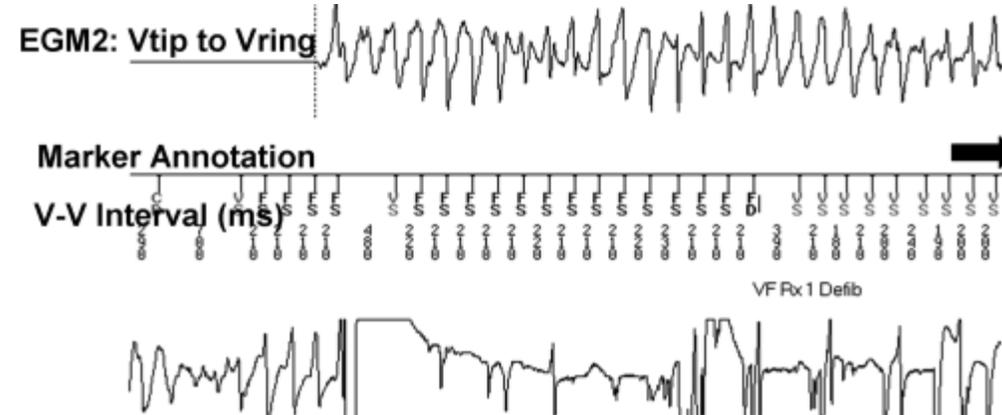
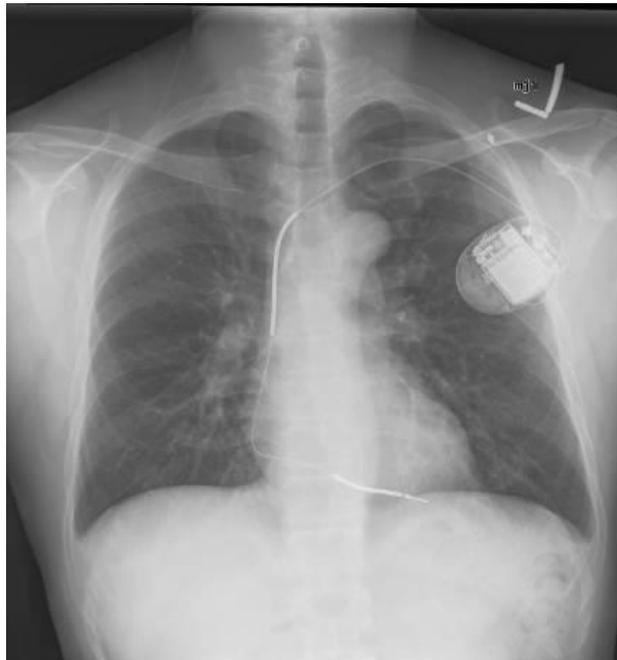


Figure 2. The day-to-day incidence of ventricular tachyarrhythmia triggering implantable cardioverter-defibrillator therapy during an eight-month observation period, with a substantial increase in event rate in the 30-day period after September 11, 2001, followed by a return to baseline.

## 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 Ehlert, 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



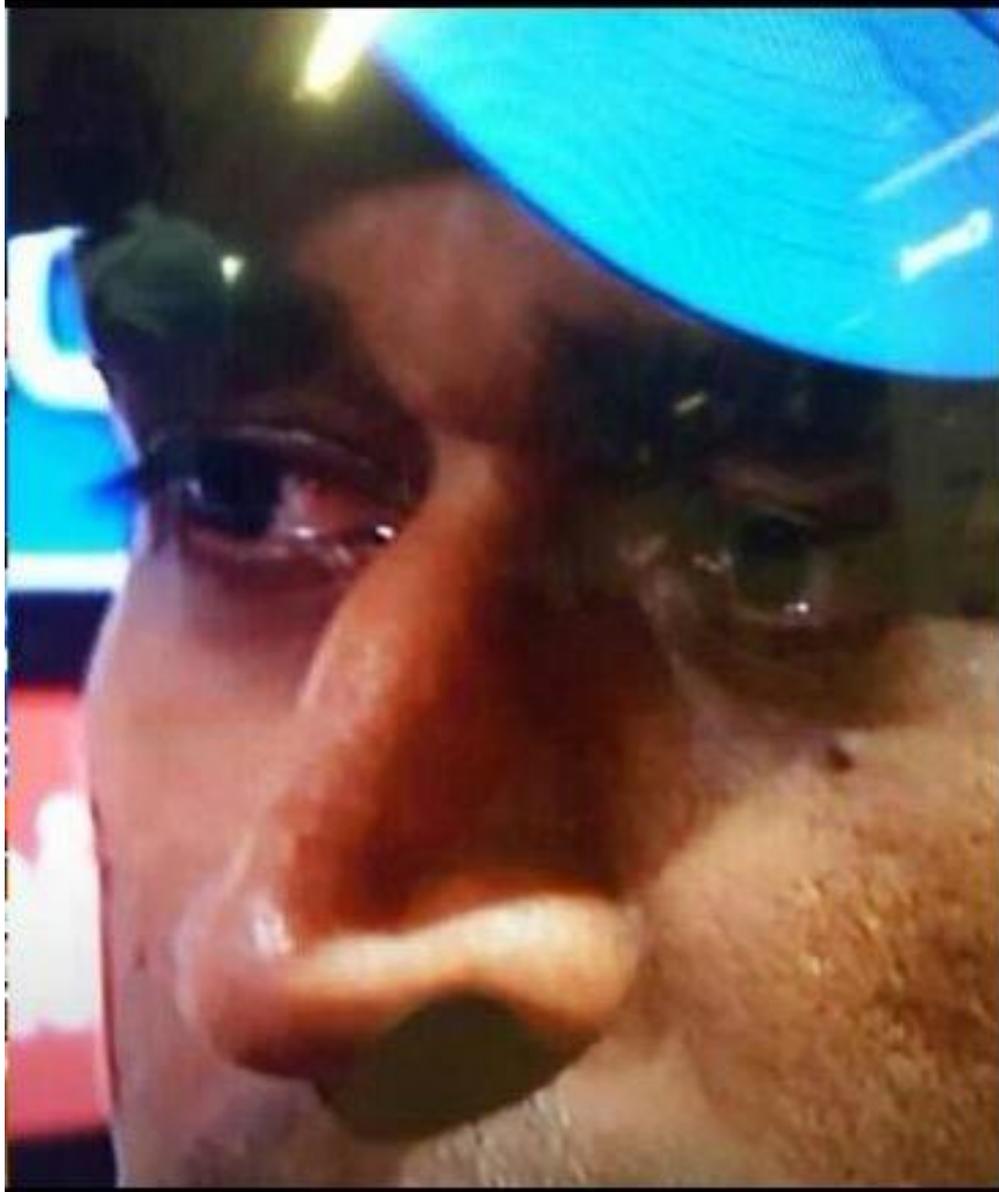
When stock markets drop, hospitalizations tend to rise.

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





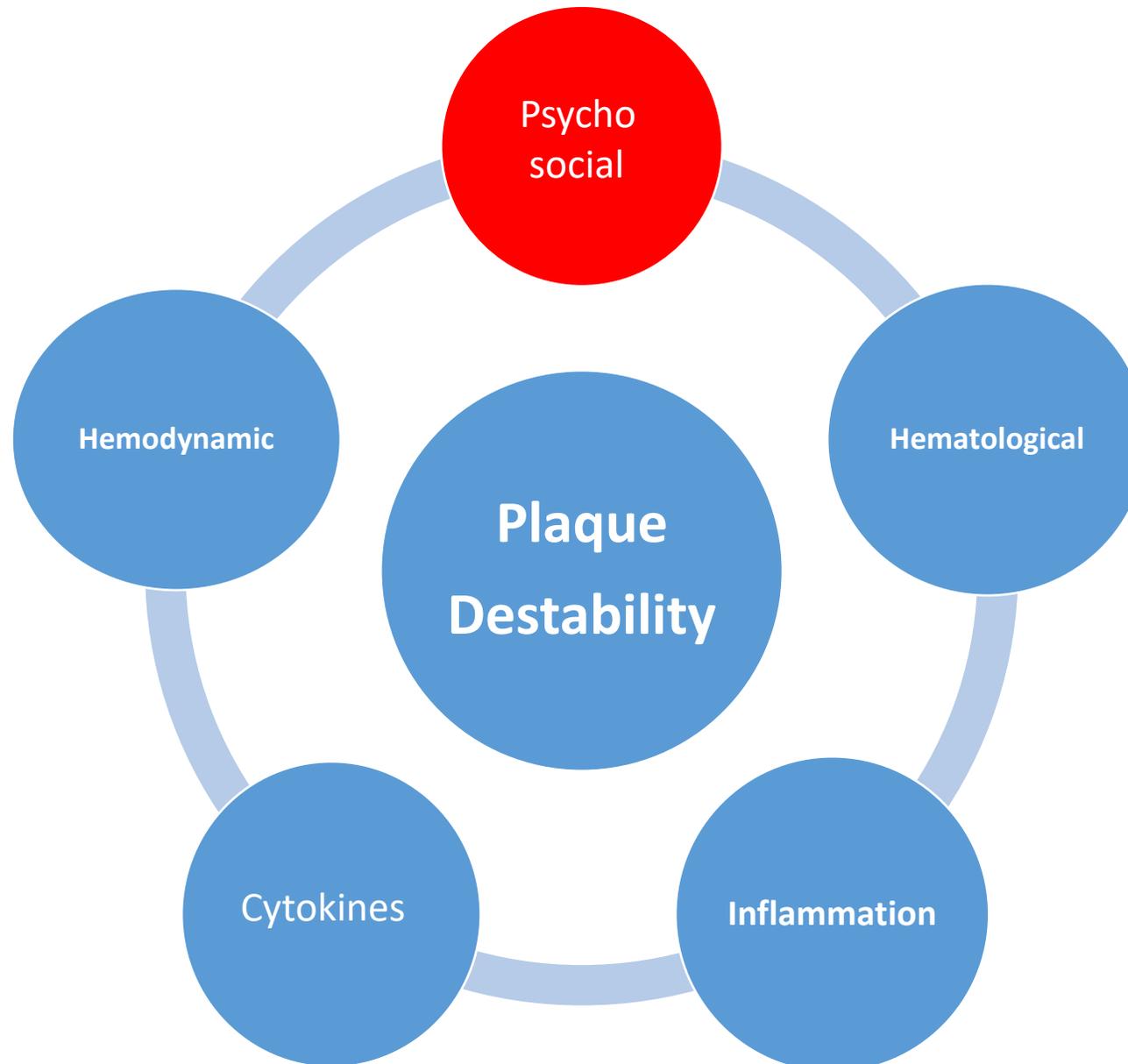
## Cricket fan dies after World Cup rout

IANIS, 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

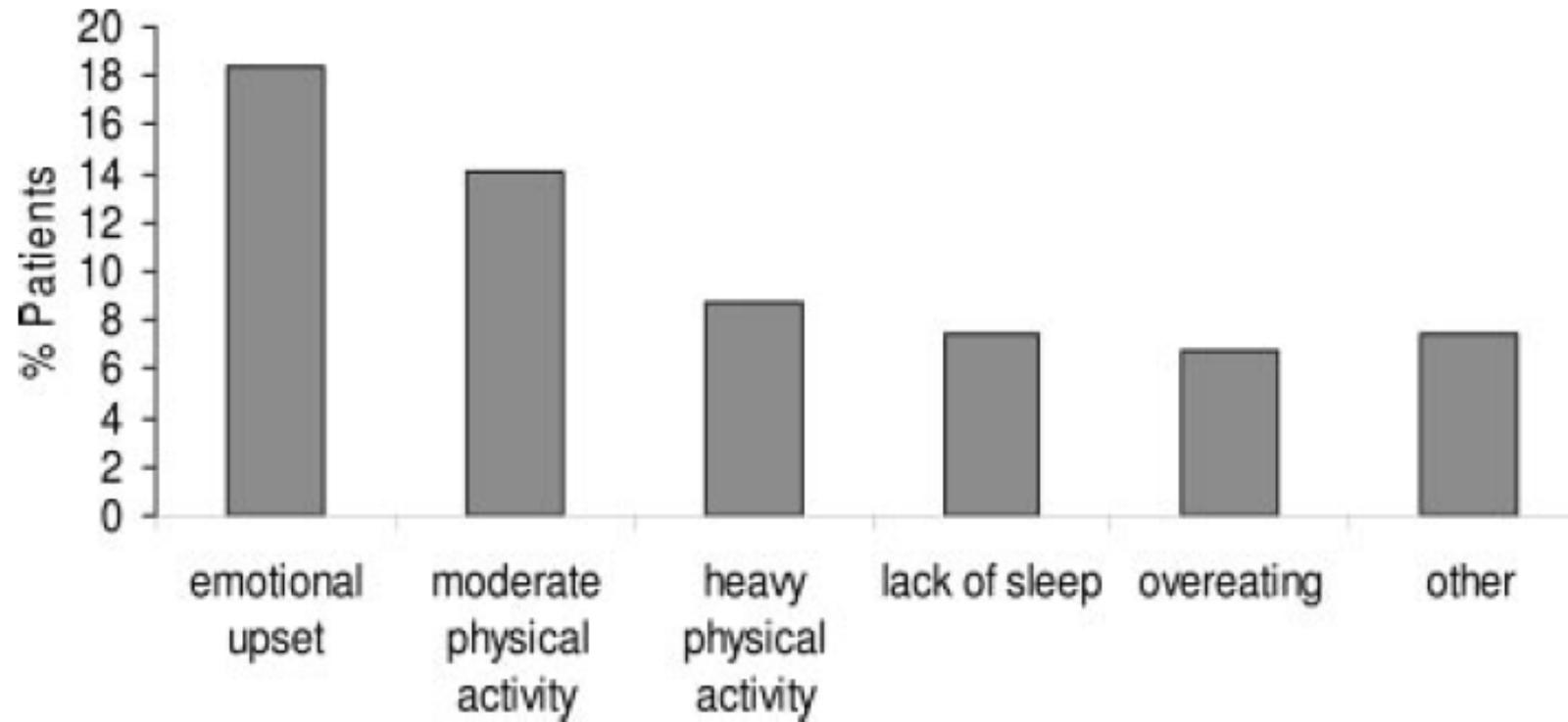


# Scientific evidence

**ONSET** (Mittleman **NEJM**1993)

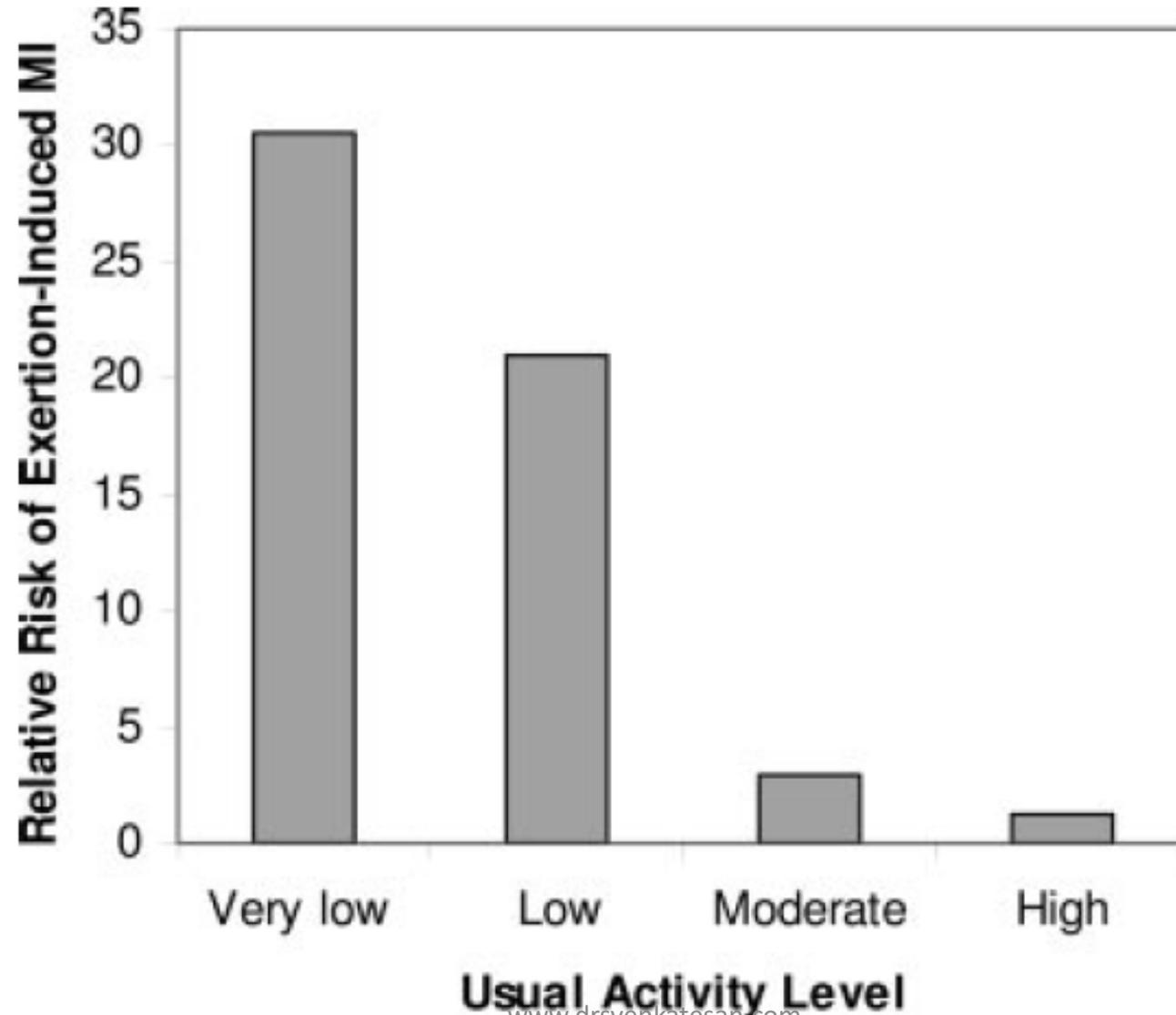
**SHEEP** (*J Epidemiol Commun Health.*  
2005)

**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<sup>27</sup> with permission from Elsevier. Copyright 1990.

# Physical exertion as trigger



# 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**

Muller JE,. *JAMA*. 1996;275:1405–1409.

Moller J, (SHEEP). *Heart*. 2001;86:387–390.

# Anger as Trigger

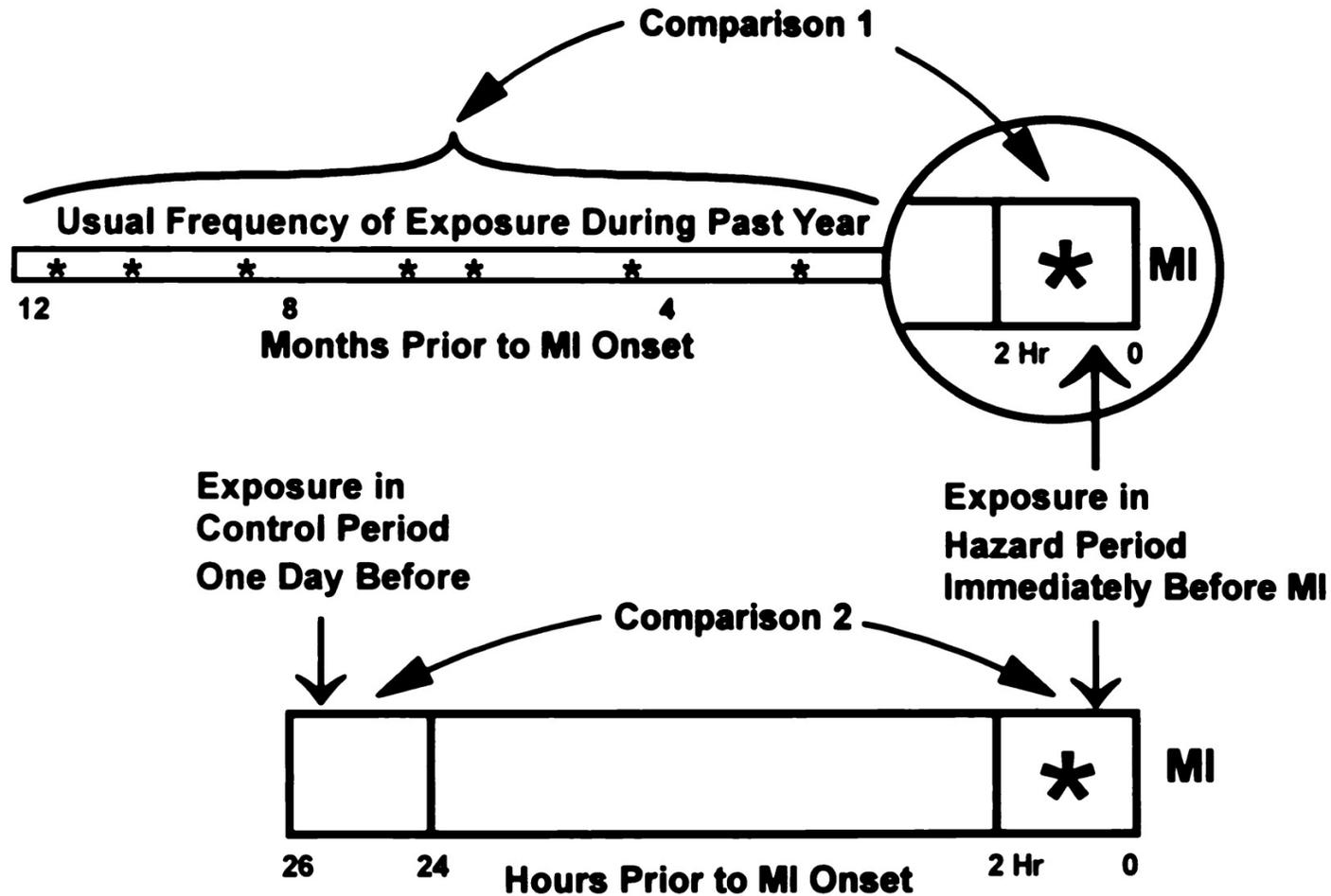
## Circulation

**Triggering of Acute Myocardial Infarction Onset by Episodes of Anger**

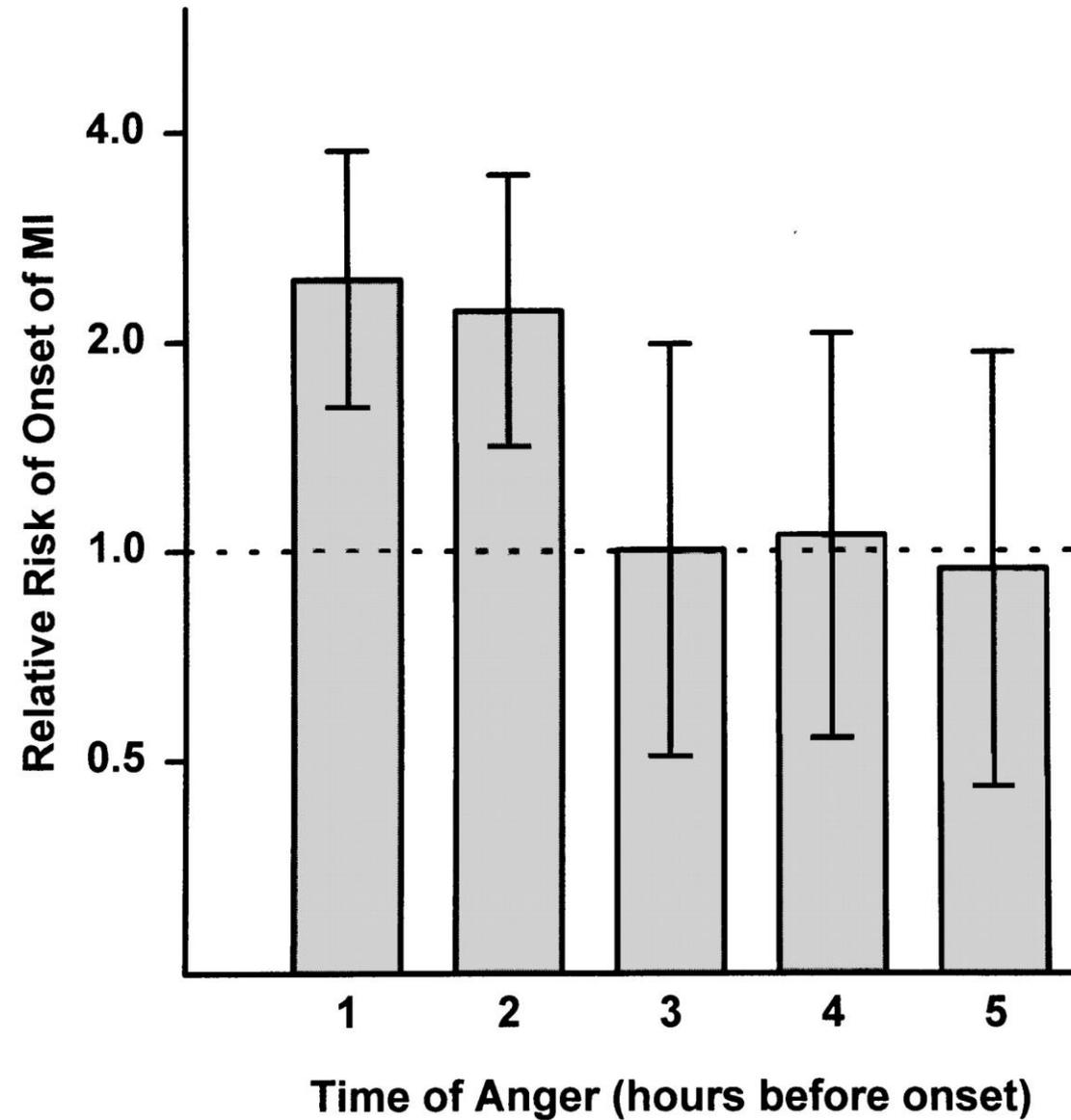
Murray A. Mittleman, MDCM, DrPH; Malcolm Maclure, ScD; Jane B. Sherwood,  
Determinants of Myocardial Infarction Onset Study Investigators

**1995;92:1720-1725**

# Case-crossover Study Design



# Timing of anger and the event



# Our experience



## ORIGINAL ARTICLE

Year : 2003 | Volume : 49 | Issue : 3 | Page : 207-210

## 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

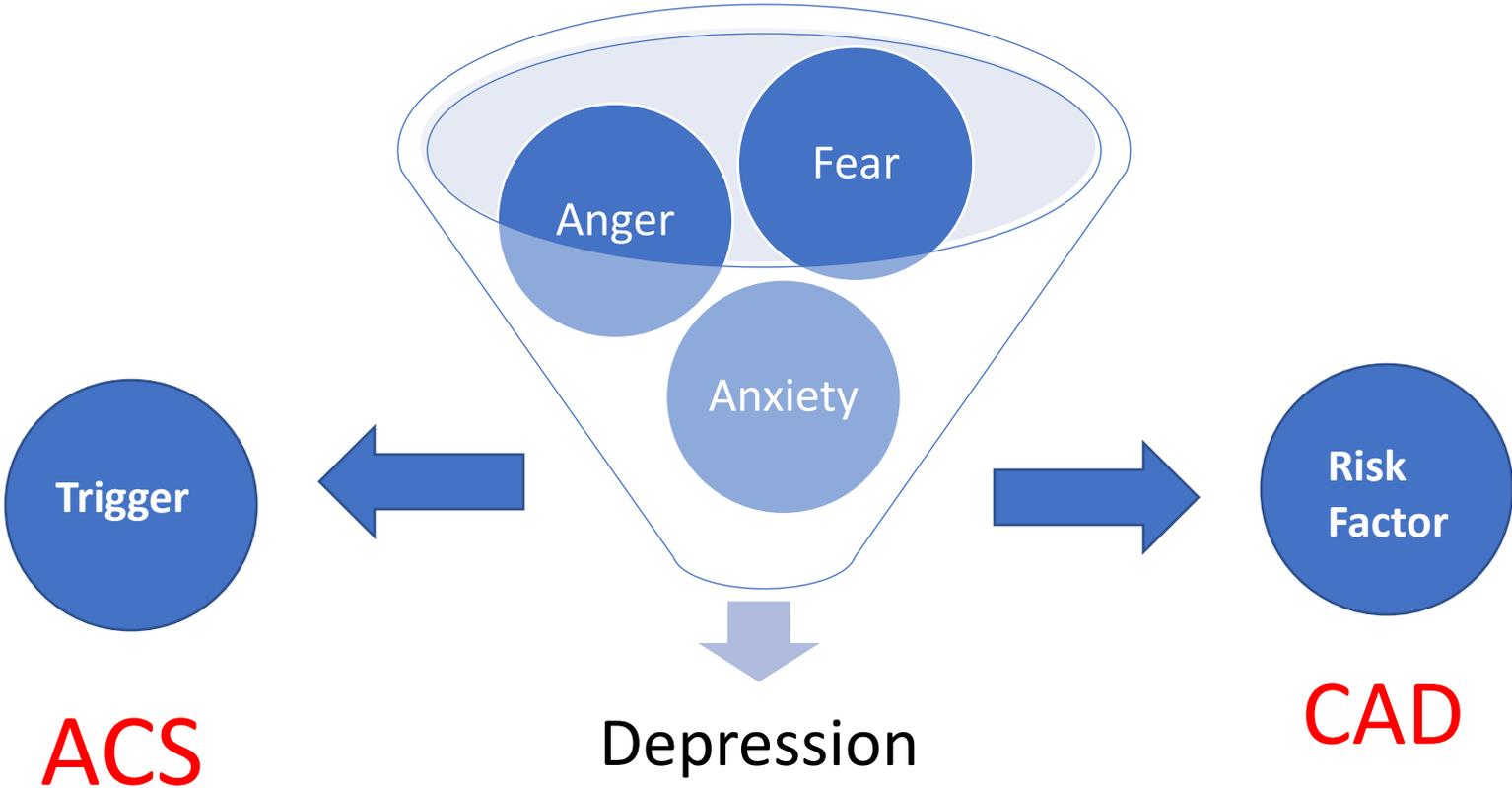
**Overwhelming epidemiological data**

**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**

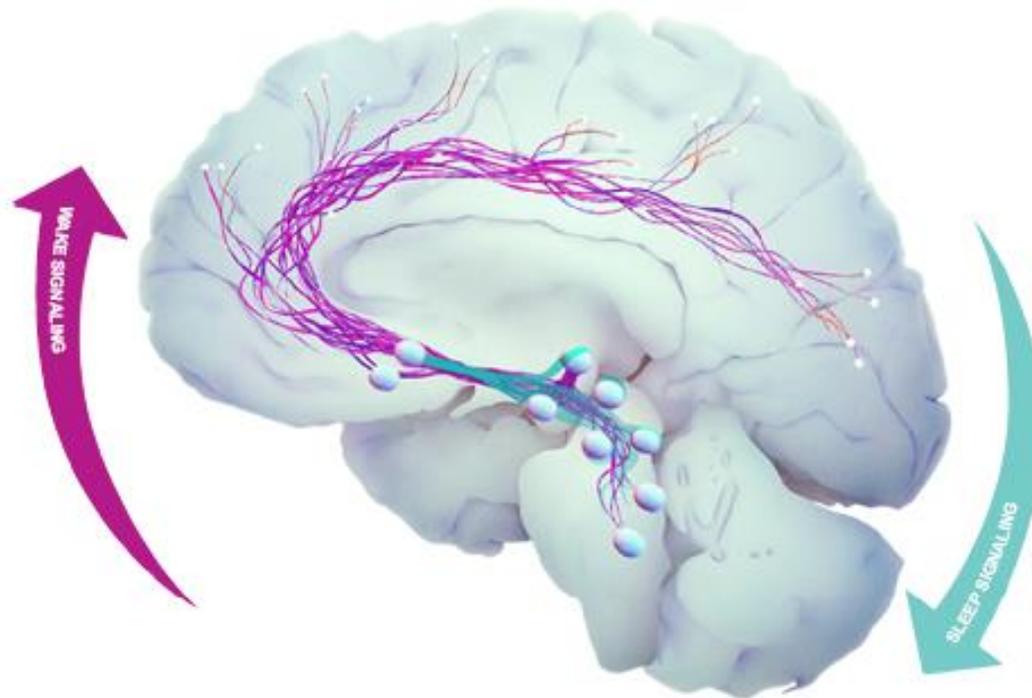
# Anger, emotion, and arrhythmias: from brain to heart

**Peter Taggart<sup>1\*</sup>, Mark R. Boyett<sup>2</sup>, Sunil Jit R. J. Logantha<sup>2</sup> and Pier D. Lambiase<sup>3</sup>**

<sup>1</sup> Neurocardiology Research Unit, Department of Medicine, University College London, London, UK

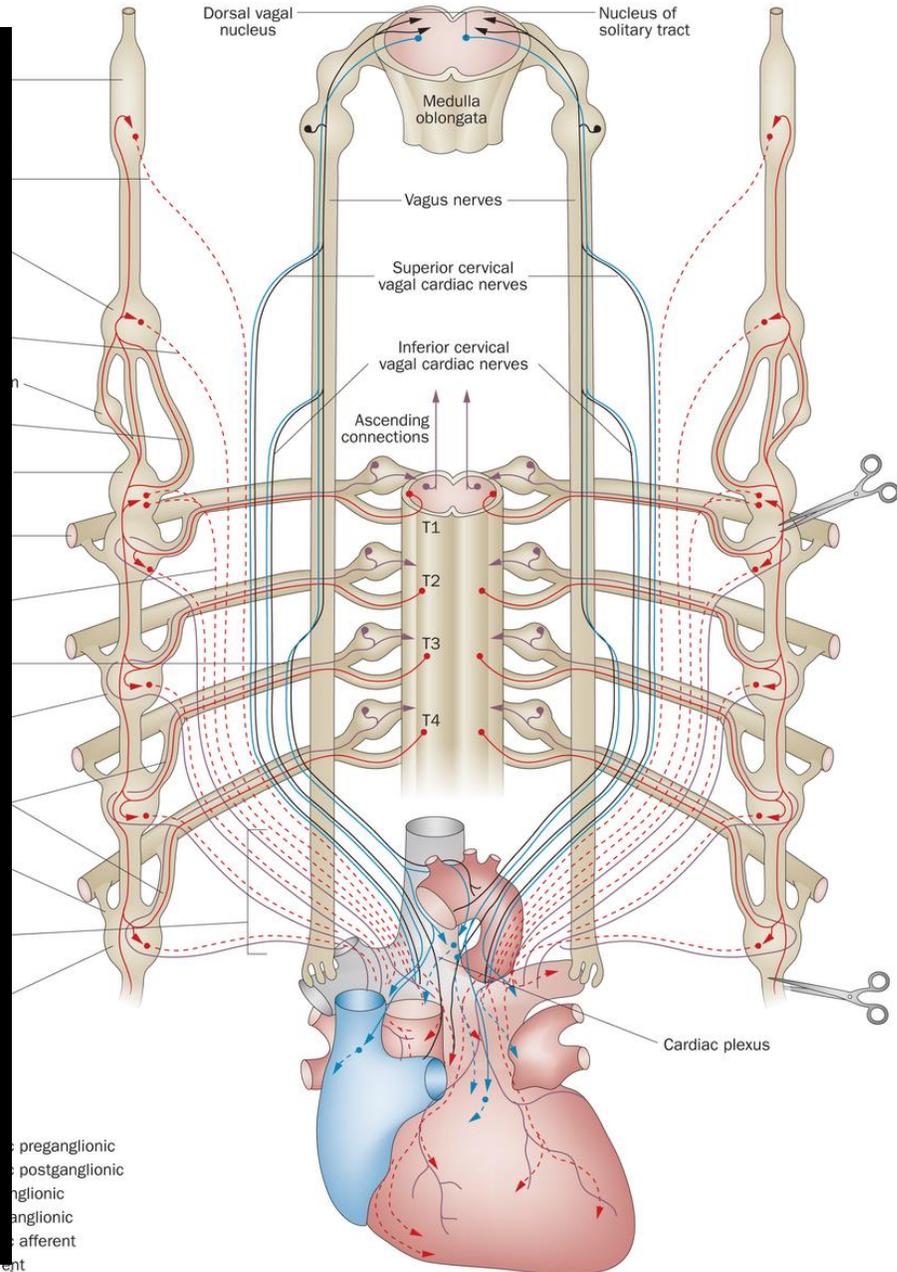
<sup>2</sup> Cardiovascular Medicine, University of Manchester, Manchester, UK

<sup>3</sup> Department of Cardiology, University College London Hospitals, London, UK

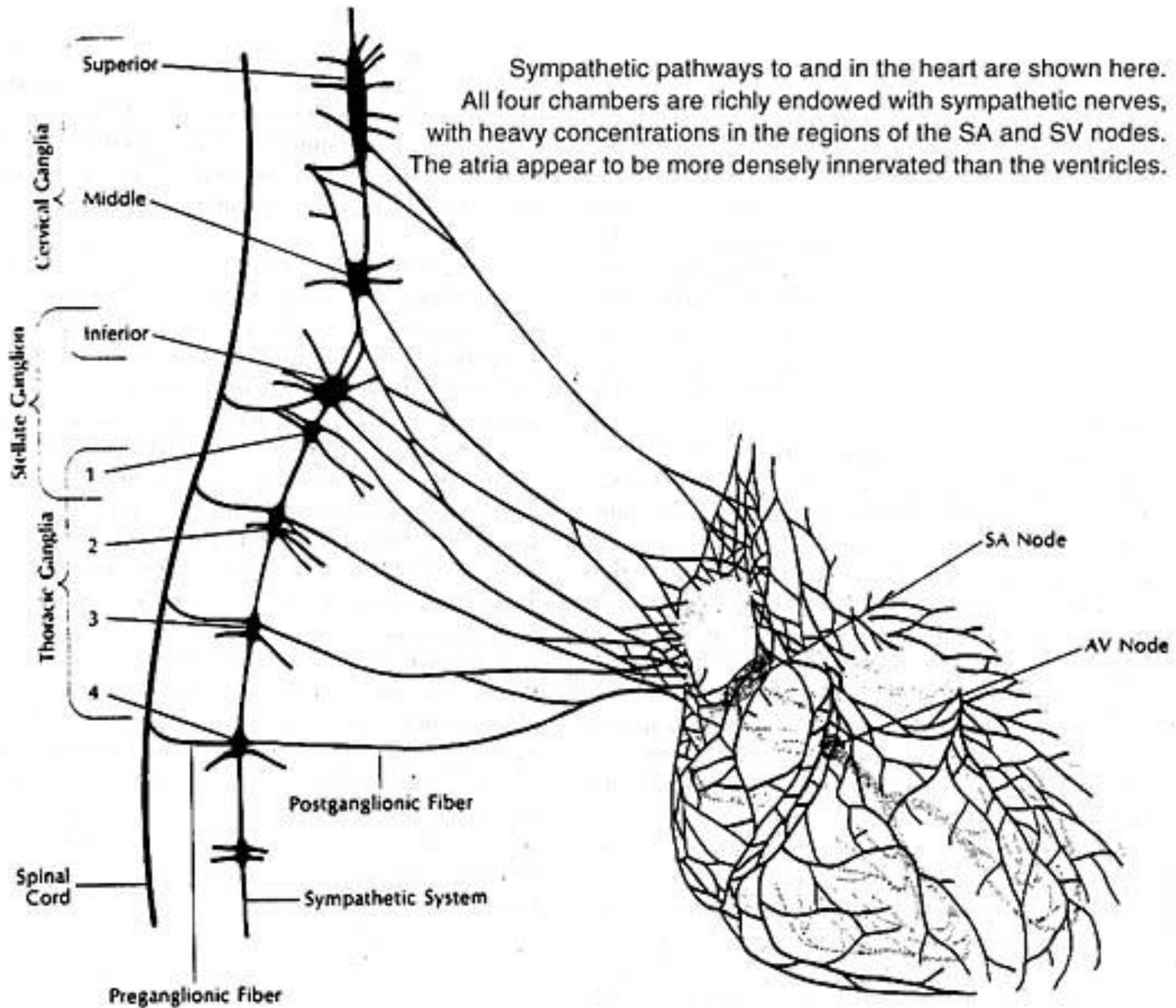


## Central sympathetic network

Cingulate gyrus  
Frontal  
Temporal  
Parietal



preganglionic  
 postganglionic  
 ganglionic  
 ganglionic  
 afferent



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)**

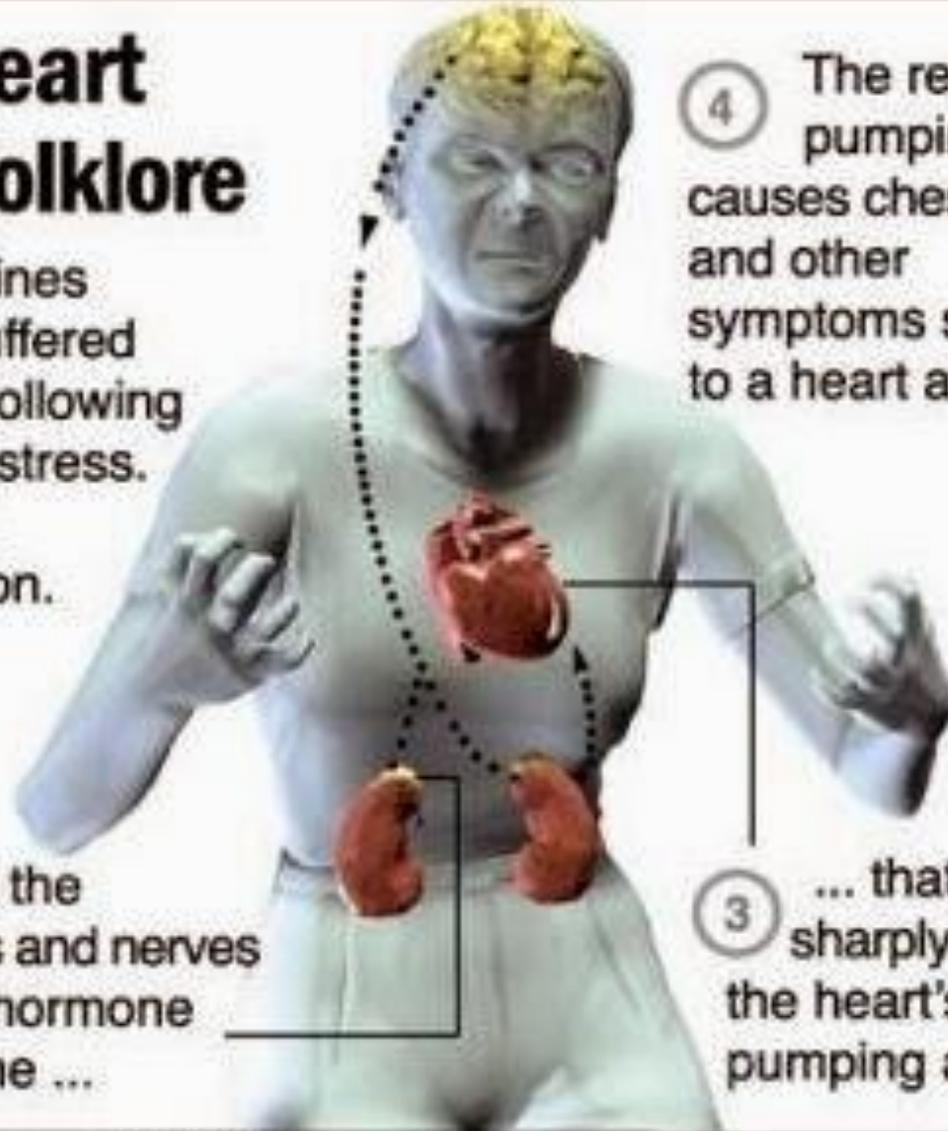
**2.Van malle 2004 psychosomatic medicine Meta analysis**

# 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 ...

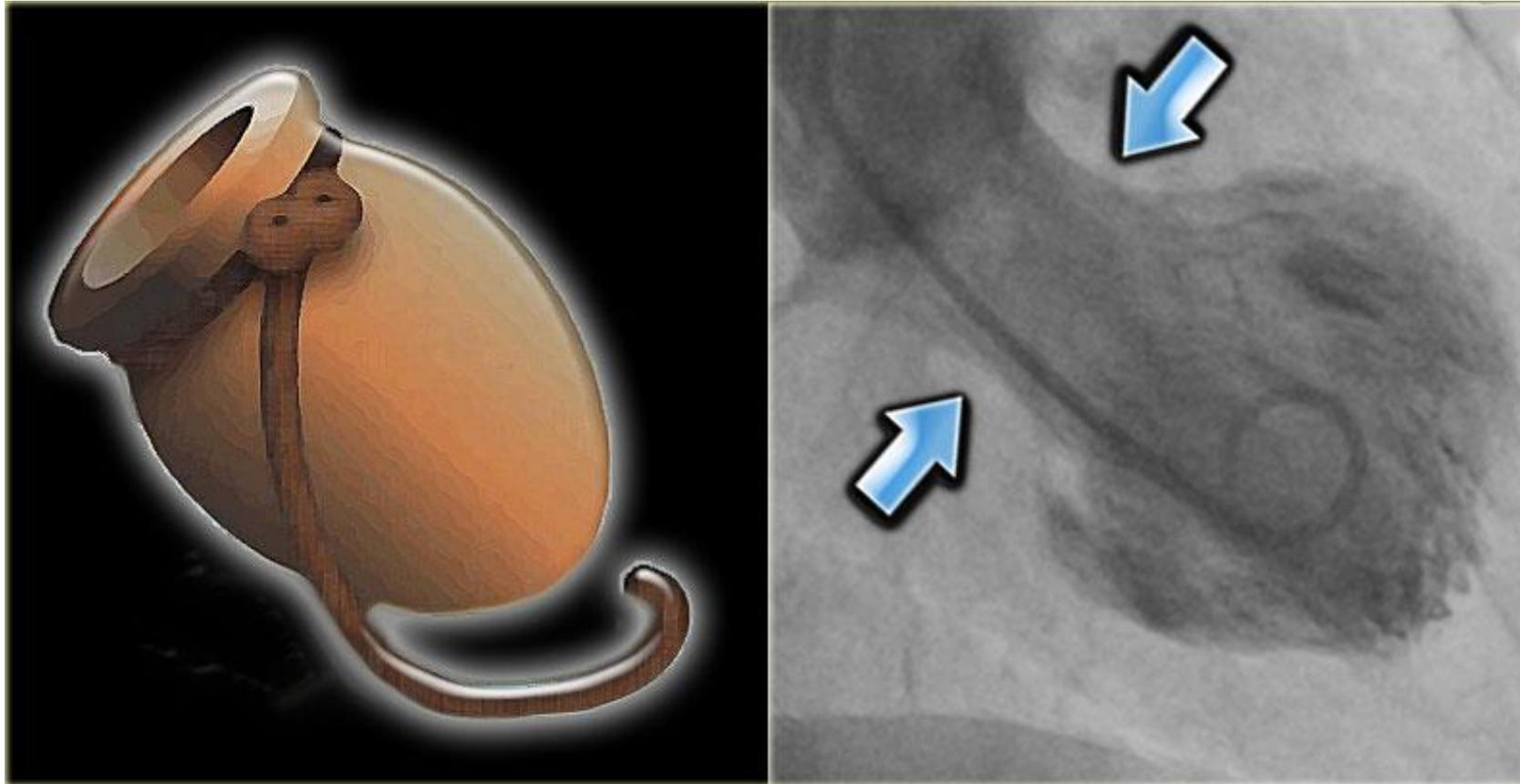
② ... stimulating the adrenal glands and nerves to produce stress hormone including adrenaline ...



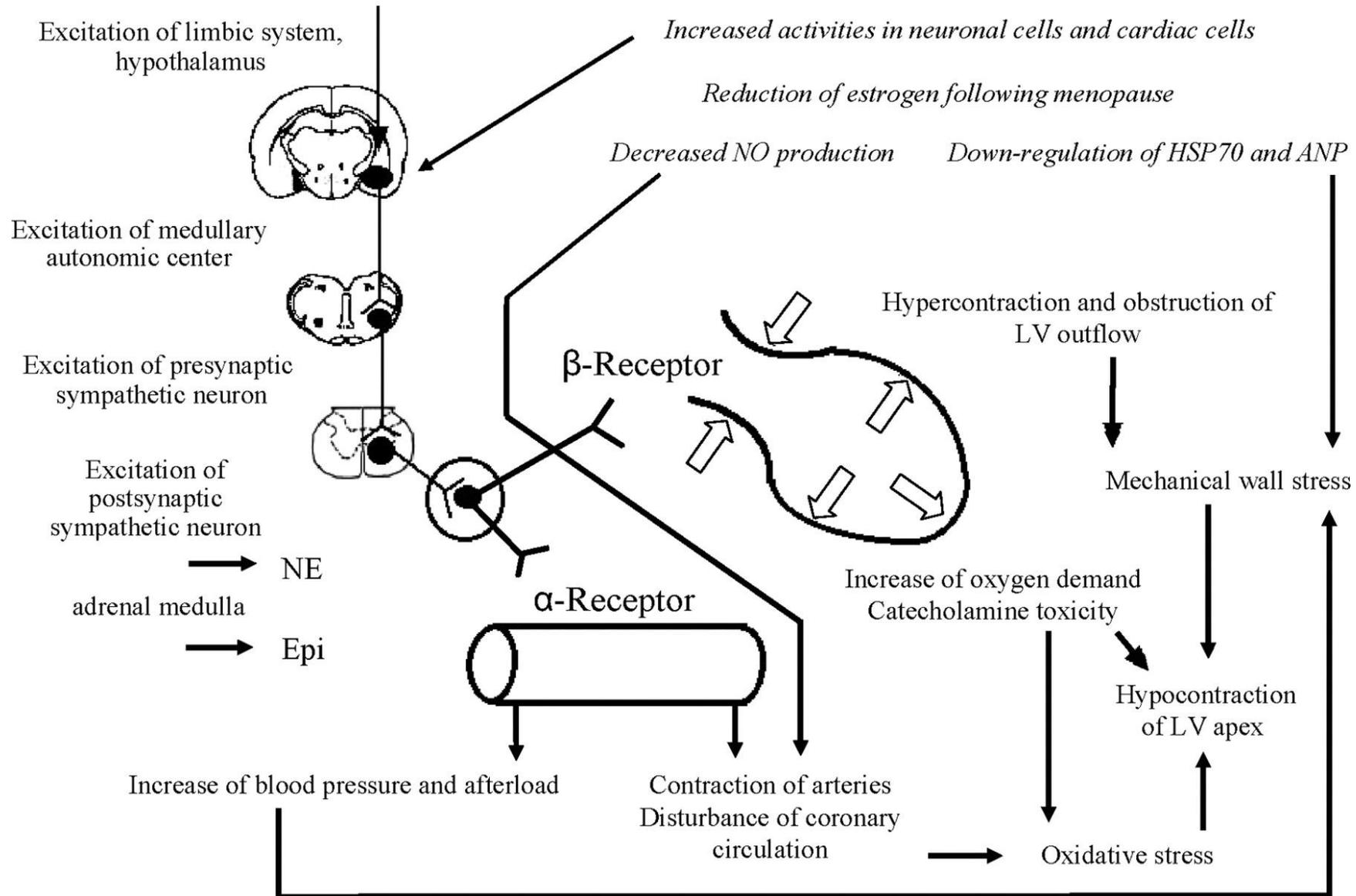
④ The reduced pumping causes chest pain and other symptoms similar to a heart attack

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

# Catecholamine toxicity



# Emotional and physical stress



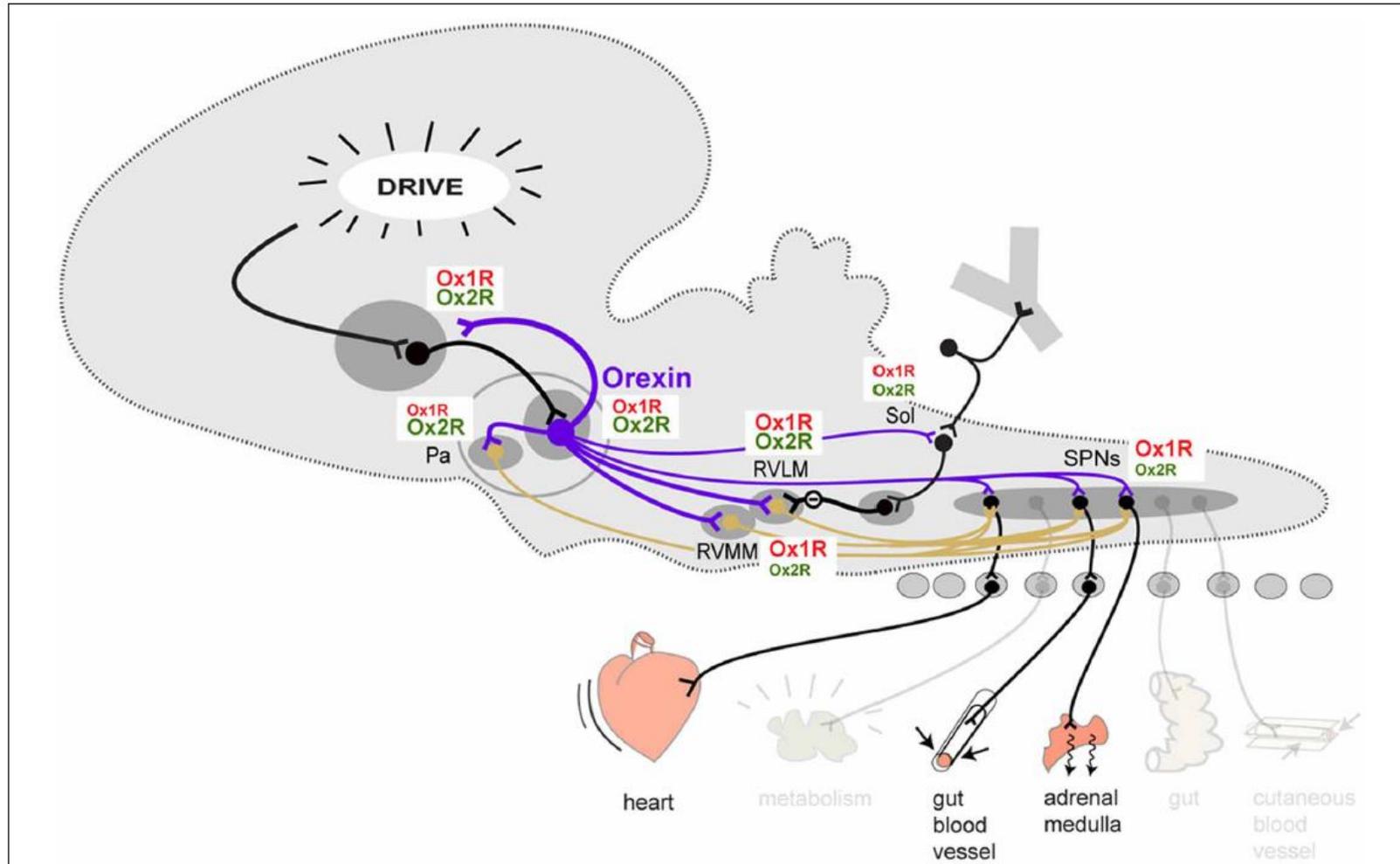
# Looking beyond catecholamine

# 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



**FIGURE 1 | Schematic overview of the orexinergic pathways involved in the descending control of sympathetic output to cardiovascular effectors.**

The contribution of Ox1R and Ox2R at each level is represented by the relative size of the Ox1R and Ox2R labels. This is a tentative representation only.

reflecting the current stage of our knowledge. Abbreviations: Pa, paraventricular nucleus of the hypothalamus; RVL, rostral ventrolateral medulla; RVLM, rostral ventrolateral medulla (plus medullary raphe); Sol, solitary nucleus; SPN, sympathetic preganglionic neurons.

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

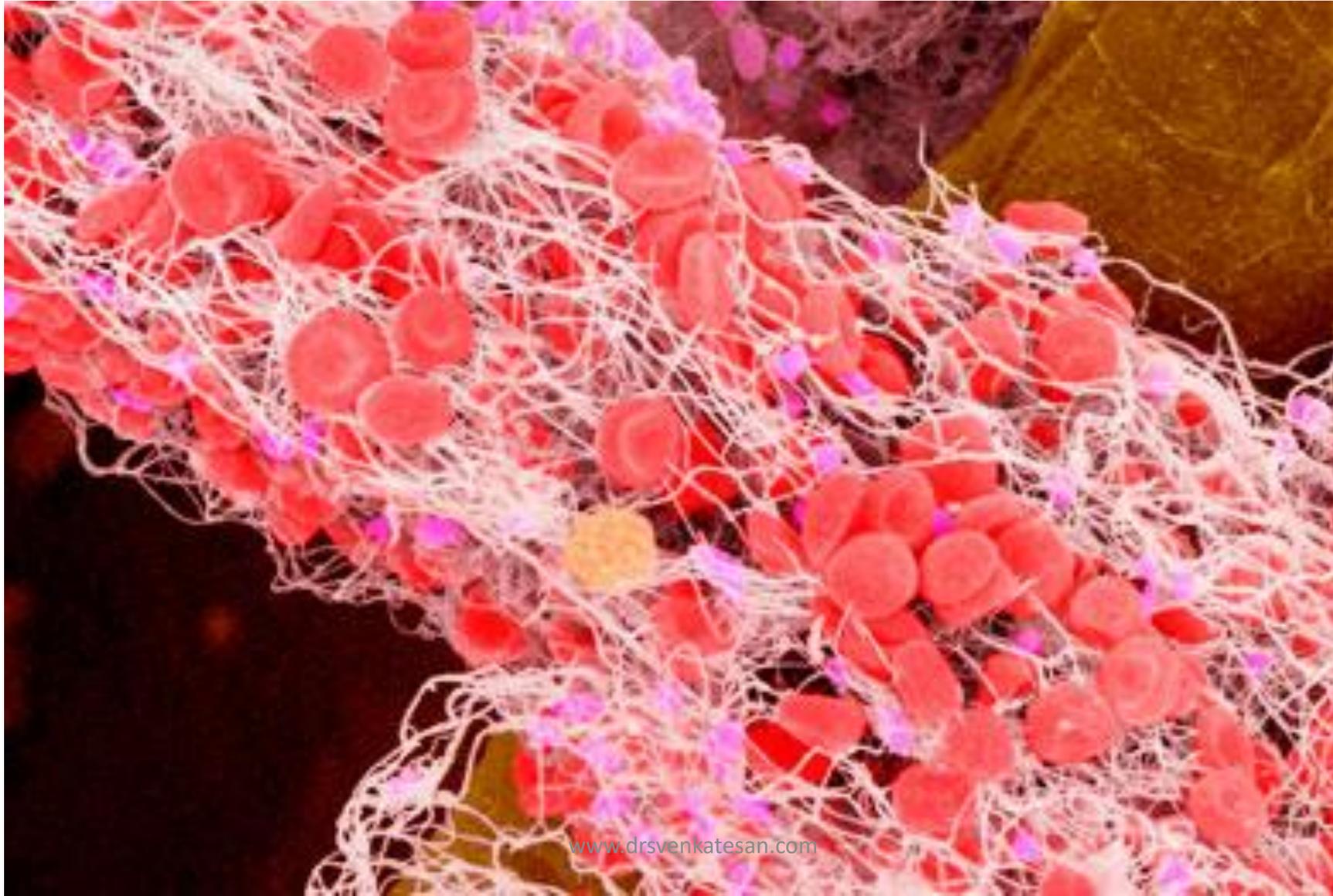
**Pro-coagulant hemostatic responses**

**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**

# Neuro electrical trigger

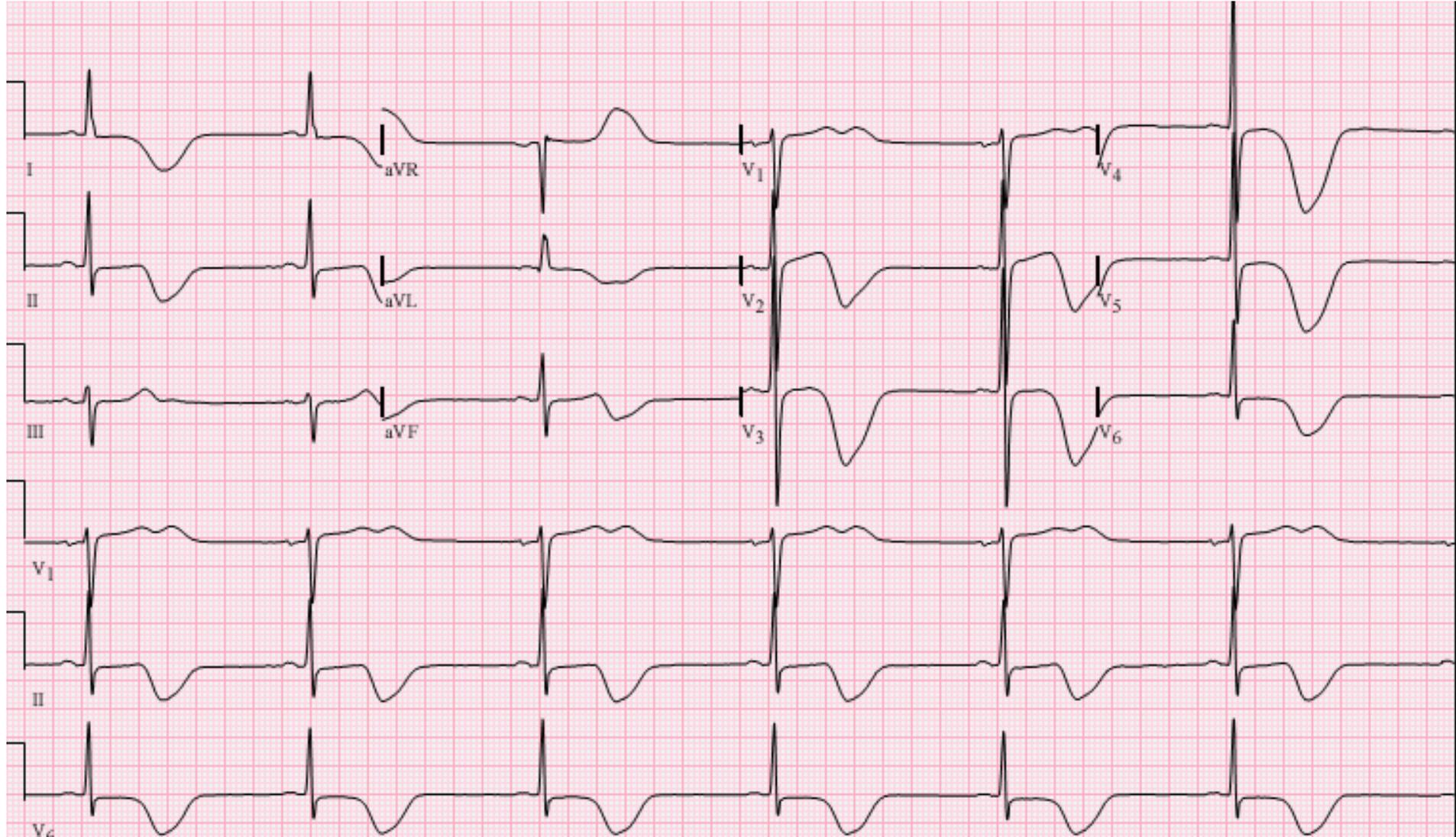
# Clinical evidence for Neuro cardiac link

**Stroke**

**Epilepsy**

**Stress cardiomyopathy**

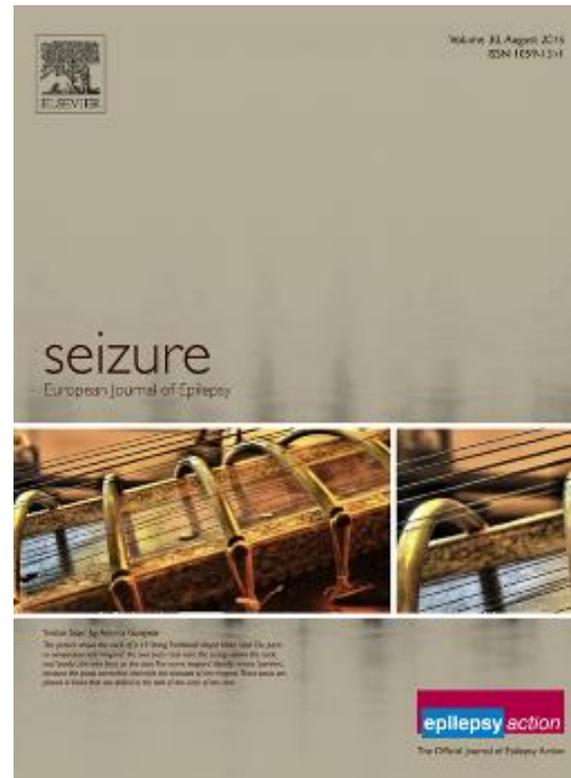
# ECG in stroke



# Holter recording during seizures



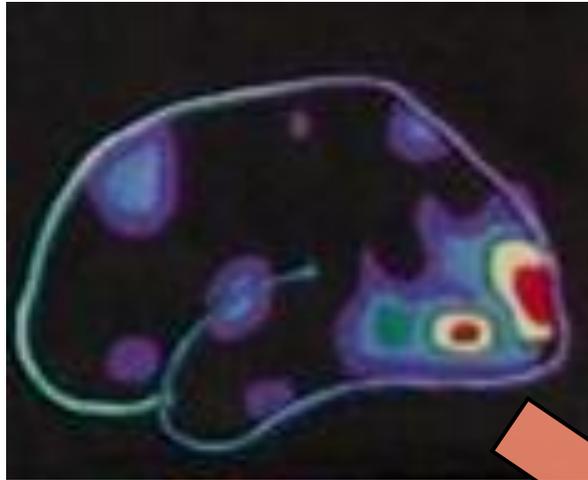
# Sudden cardiac deaths during seizures The mystery Ictal asystole and VF



[Seizure induced ventricular fibrillation: A case of near-SUDEP](#) Monica Ferlisi<sup>a</sup>, Ruggero Tomei<sup>b</sup>, Monica Carletti<sup>b</sup>, Seizure Volume 22, Issue 3, April 2013, Pages 249–251

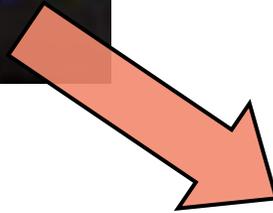
# Mechanism of primary VF

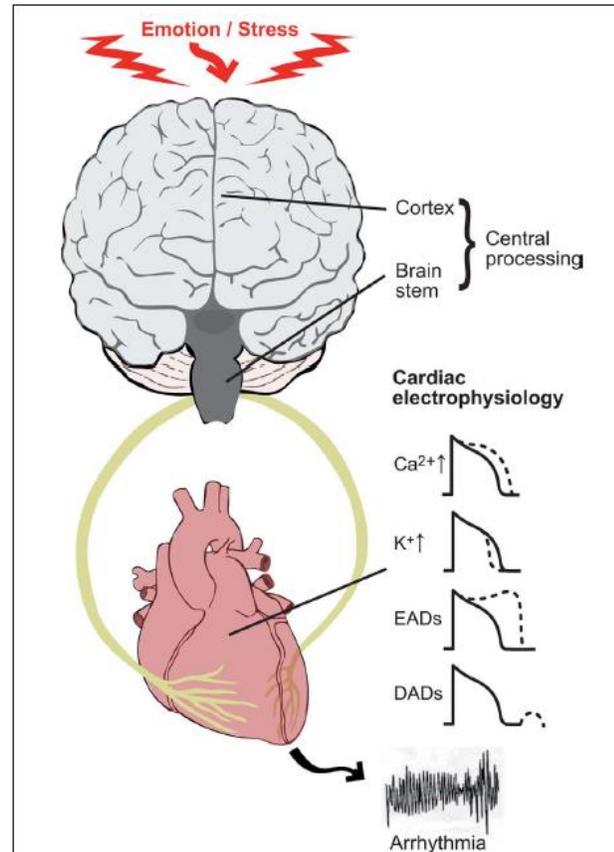
## Is the heart a neurological end organ ?



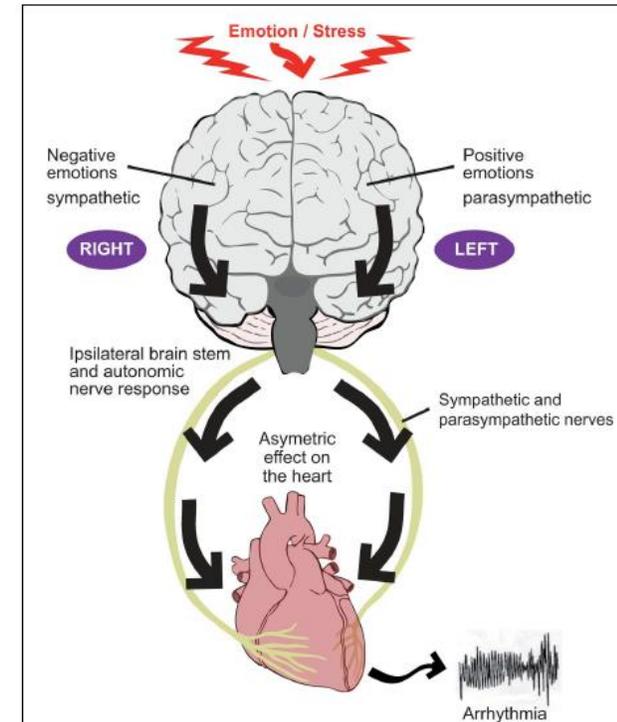
Paraventricular nucleus

Triggers VF in animals





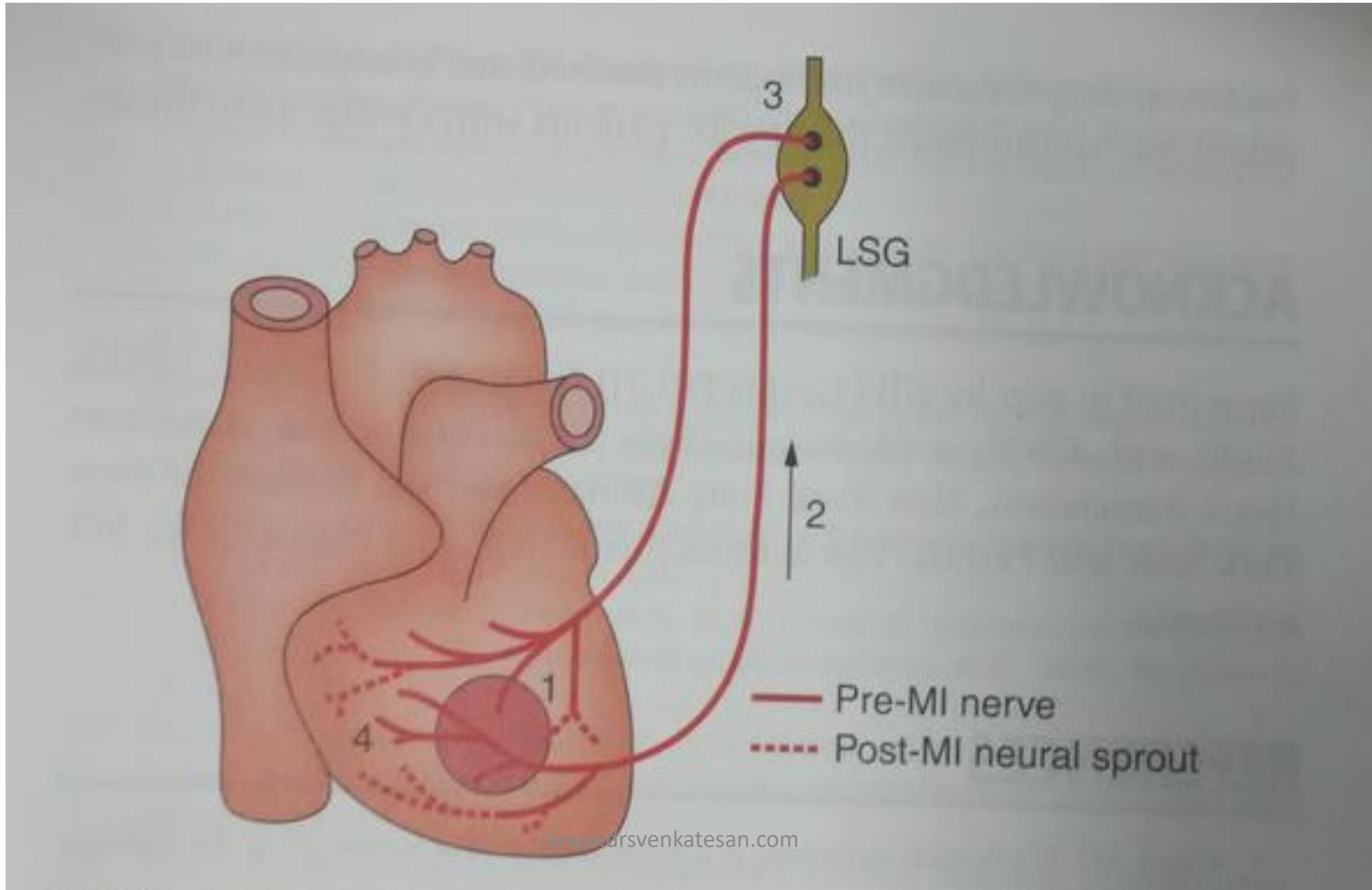
**FIGURE 1 |** The theme of this review is to consider the brain and heart as an interactive unit and its role in the generation of ventricular arrhythmias. Key components are (1) the electrophysiological changes occurring in the myocardium as a result of autonomic nerve stimulation; (2) the modulatory role of the sympathetic and parasympathetic nerves which tend to oppose and balance each other (3) central neural processing of emotional input and afferent input from the heart and circulation. Sympathetic nerve stimulation acting through  $\beta$ -adrenergic receptors influences a number of ion channels and transporters in cardiac myocytes.



**FIGURE 2 |** The two components of the autonomic nervous system, the sympathetic nerves and parasympathetic (vagus) nerves tend to act in a reciprocal manner such that, for example, an increase in sympathetic activity is accompanied by a decrease (or lesser increase) in parasympathetic activity. Evidence suggests that the right cerebral hemisphere is predominantly concerned with negative emotion and sympathetic activity, whereas the left hemisphere is predominantly concerned with positive emotion and parasympathetic activity. Autonomic nerve traffic from the brain to the heart is mainly ipsilateral between the brainstem and heart. There is also some degree of lateralization of the distribution of the right and left autonomic nerves on the heart. These considerations form the basis for the laterality hypothesis whereby central neural processes may be represented asymmetrically on the heart and thereby induce inhomogeneous repolarization and be proarrhythmic.

## Para sympathetic vs sympathetic . Right vs left

# Neural sprouting



# Neural sprouting – S 100 positive fibrotic myocardium



FIGURE 38-20. S100-positive nerve fibers in ventricular tachycardia (VT) origin of [www.drsvenkatesan.com](http://www.drsvenkatesan.com)

# Evidence for benefits with Neuronal blockade

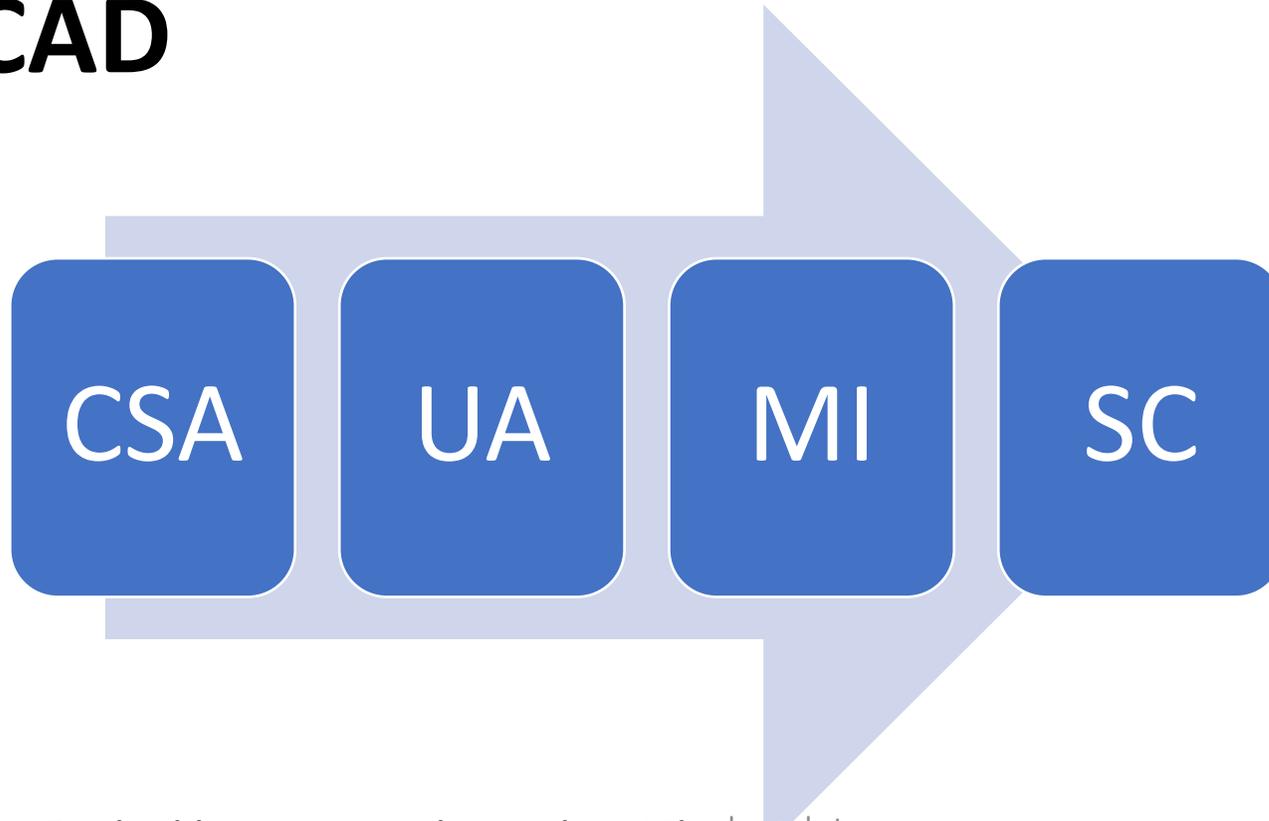
**Cervical sympathectomy**

**Beta blockers**

**Post transplant hearts**

# Beta blockers

Key role Entire spectrum of CAD



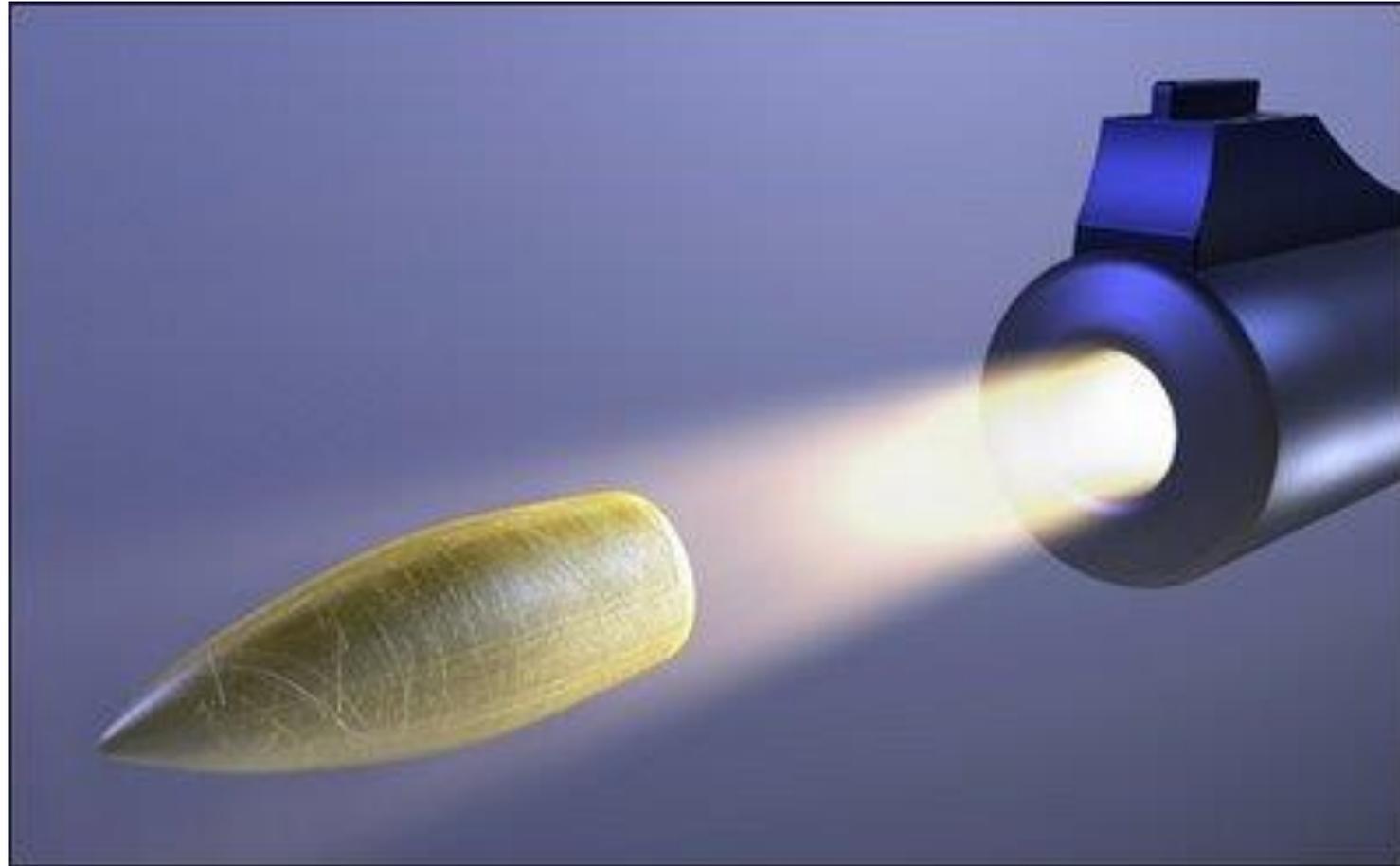
Backed by mega trials , without dispute [www.drsvenkatesan.com](http://www.drsvenkatesan.com)

# 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?* www.dovekateer.com

# Emotional stress testing

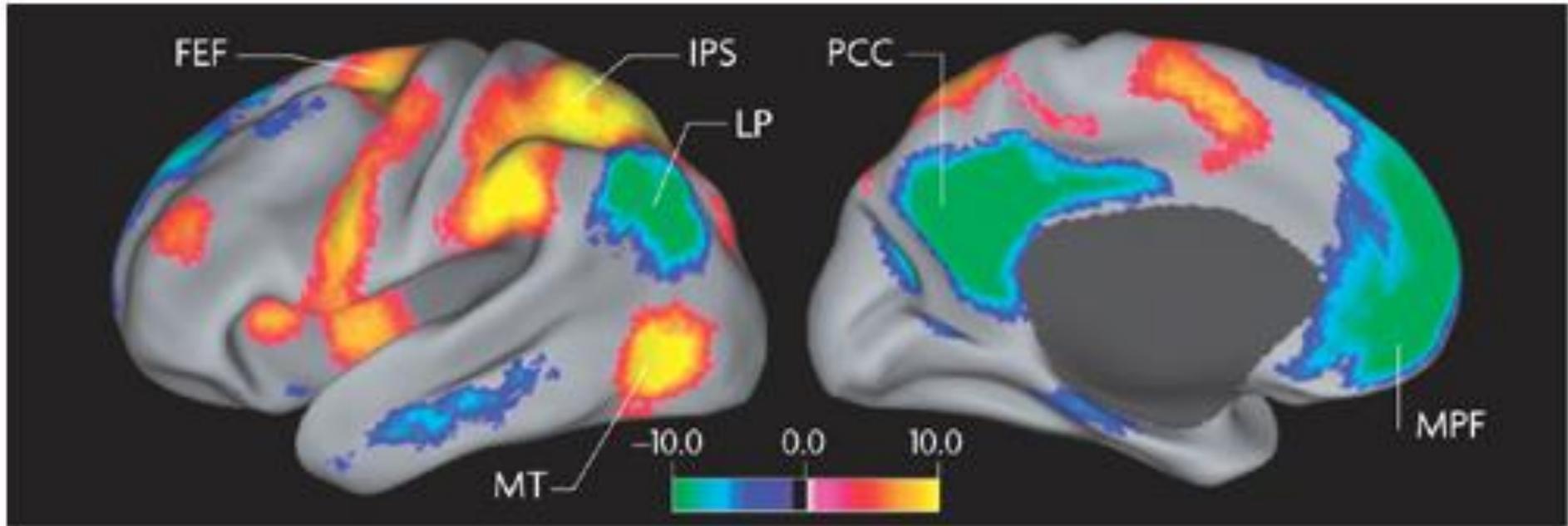
ST depression

Wall motion defect

*Newer protocols are defined*

# PET imaging of emotions





Nature Reviews | Neuroscience

**In Search of  
Coronary-  
Prone  
Behavior**  

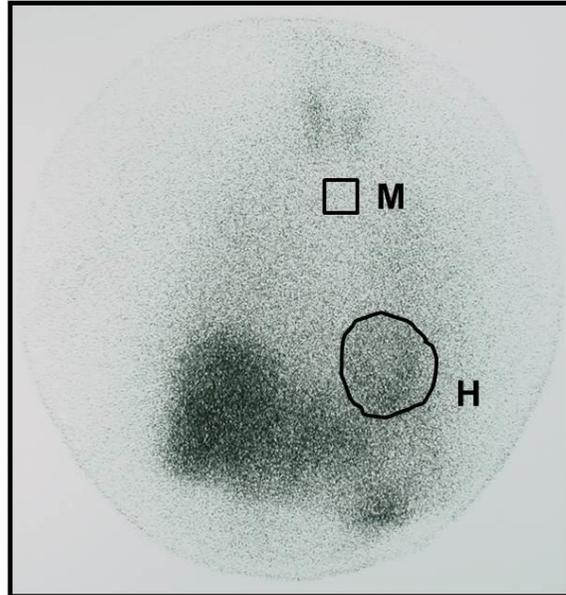
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**Beyond Type A**

**Edited by  
Aron W. Siegman  
Theodore M. Dembroski**

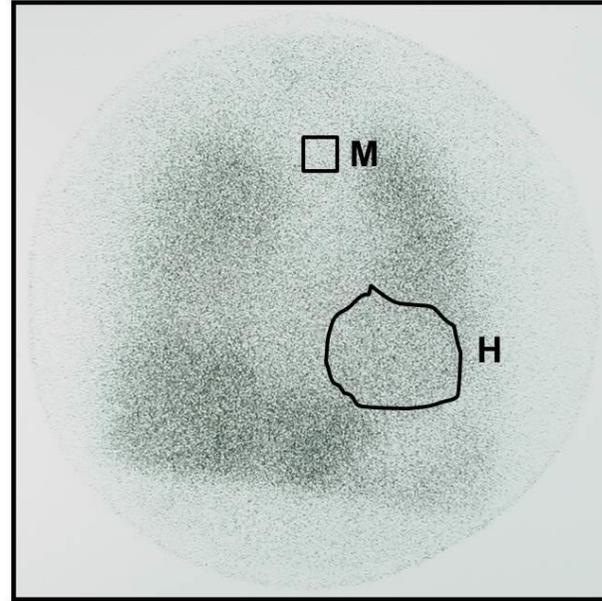
# Catecholamine Imaging

NYHA I



H/M: 2.34, WR: 15%

NYHA III



H/M: 1.45, WR: 39%

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

***Reduced myocardial stores, Rapid washout, and spill over in CHF***

# Treating Depression and prevention of cardiac events

- **SAD - HEART**
- **CREATE**
- **MIND IT**

**Markovitz Mathews psychosomatic medicine ,1991**

**Musselman , Manatunga Am J of psychiatry ,1997**



# 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

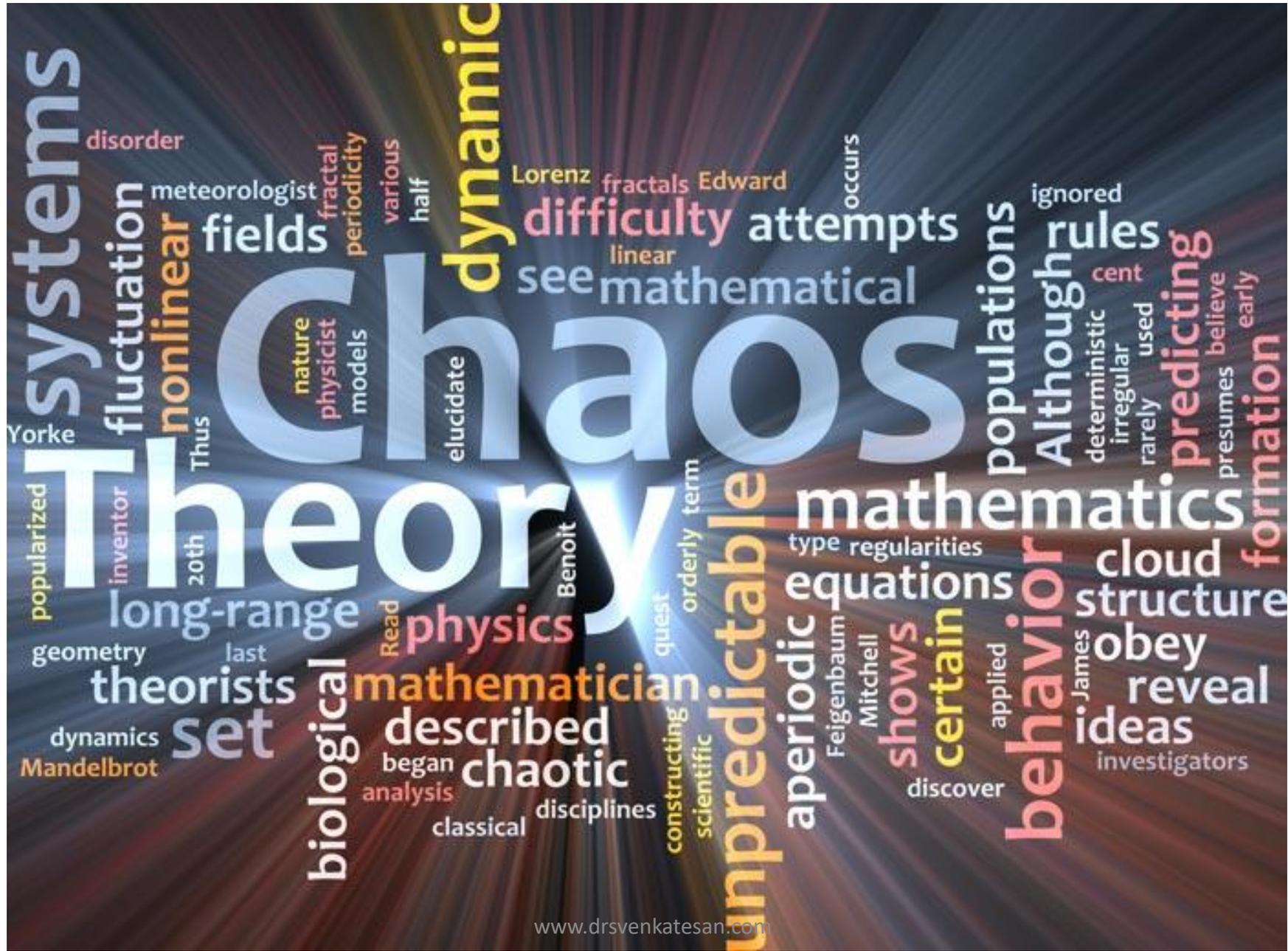
- **Strong neuro cardiac link in ACS exist.**
- **Triggers are vital**
- **Baseline risk factor is the key**
- **Triggers per-se for fatality seems rare.**
- **Standard medical treatment is crucial**

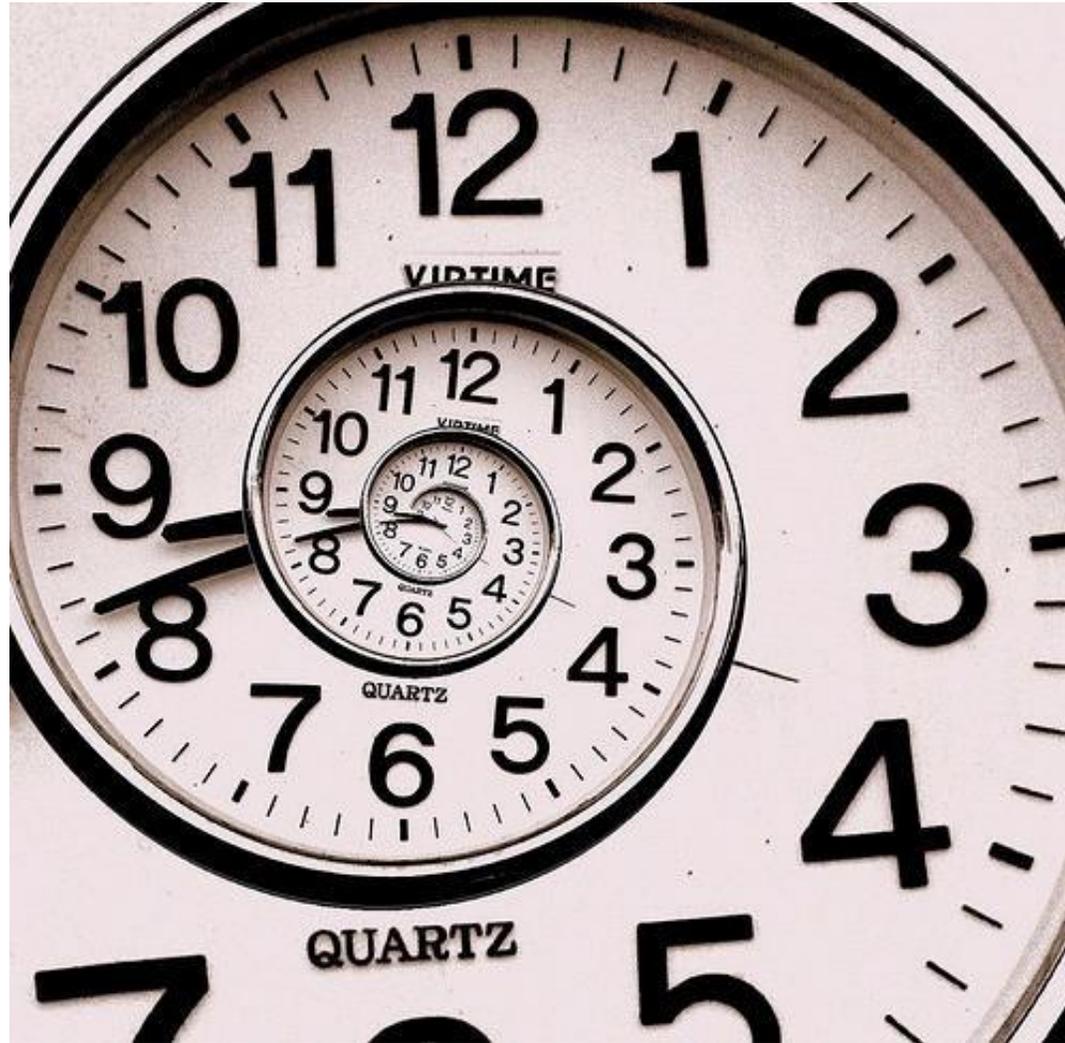
**Can we eliminate these triggers  
Completely ?**

**Emotions Integral part of life**

**Only a fraction transform to  
clinical events**

*What is the missing link ?*





- Time ?
- Metaphysics ?
- Heisenberg ?

***Knowledge will evolve . . .***

***“Meanwhile . . . It’s highly likely a **cool mind** can definitely prevail over the heart”***



**Thank you**