# BRIEF OUTLINE

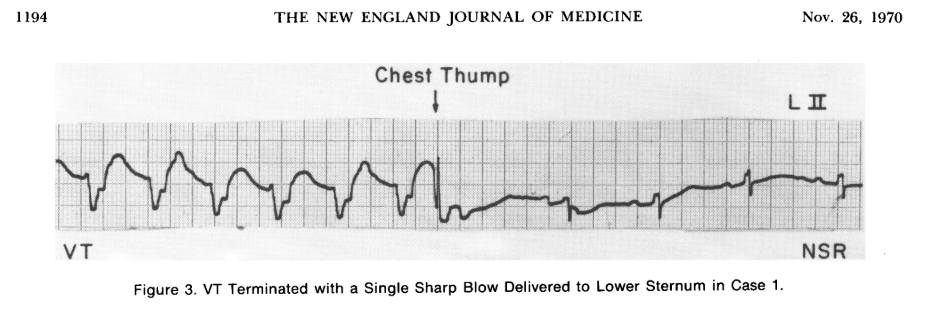
1. Title - A History of Sudden Cardiac Death
2. Important concepts - role of ANS and dysrhythmias, measurement of tone
3. Objectives - mechanism behind SCD triggers, ANS instability may be a risk factor for SCD
4. Outline - current model of SCD, relevant anatomy and physiology, ventricular substrate, triggers
5. History of SCD – MacWilliams to Lown
6. Advent of the CCU (Lown)
7. Susceptibility to VF – Lown/Rabinowitz hypotheses on neural activity changing VF threshold
8. Anatomy of the neurocardiac axis – Armour, Natelson
9. Sympathetic tone leads to increase risk of VF
10. Vagal tone can be protective
11. Heart rate variability as an integrated measurement of ANS on the sinoatrial node
12. Measurement of HRV – frequency domain as an insight into sympathovagal balance, Akselrod paper
13. Sympathovagal interaction – example using Schwartz accentuated antagonism
14. Review HRV/ANS topics thus far
15. Ventricular substrate – innervation of the heart, ventricular mass, effect of ischemia (Zipes)
16. Triggers – epidemiology studies (Leor, Rahe, Greene, Muller)
17. Autonomic risk – ATRAMI, Dyx papers, canine model of VF susceptibility (Billman)
18. Summary

# DETAILED NOTES ON THE HISTORY OF SUDDEN CARDIAC DEATH

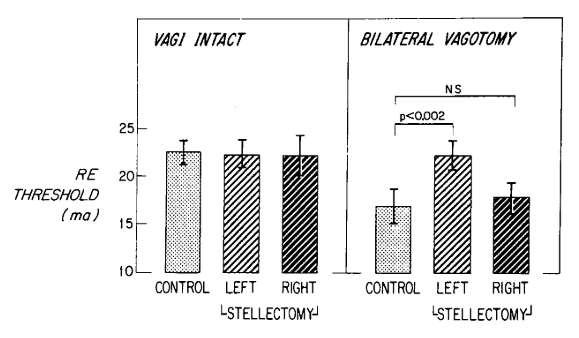
## Introduction

1. Title
   1. A History of Sudden Cardiac Death
   2. “Why did he die on Monday instead of Tuesday?” ~ Zipes
2. Important concepts
   1. Role of the autonomic nervous system in the development of dysrhythmias
   2. Measurement of autonomic tone, e.g. sympathovagal balance
   3. Objectives
      1. Mechanisms behind “triggers” that cause SCD
      2. Autonomic instability may independently be a risk factor for SCD
3. Outline
   1. Current model of sudden death
   2. Relevant anatomy and physiology of the ANS
   3. Ventricular substrate
   4. Modifiers and triggers that lead to sudden death

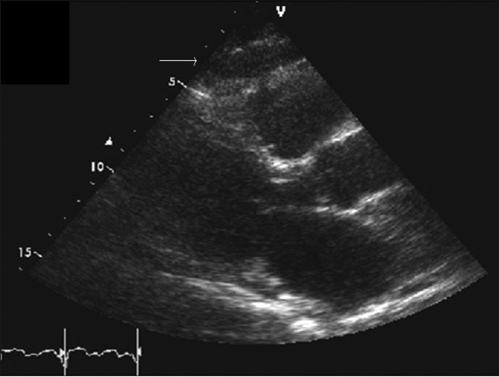
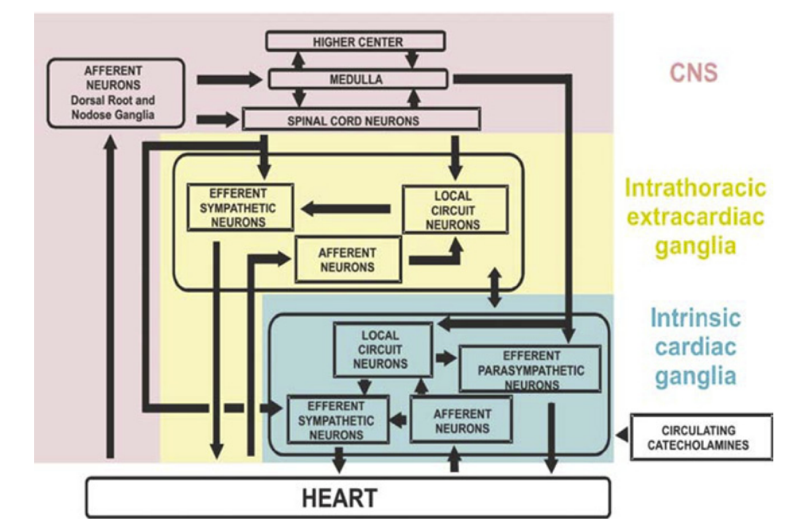
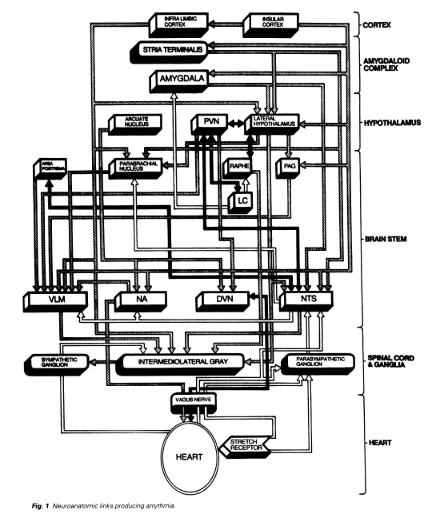
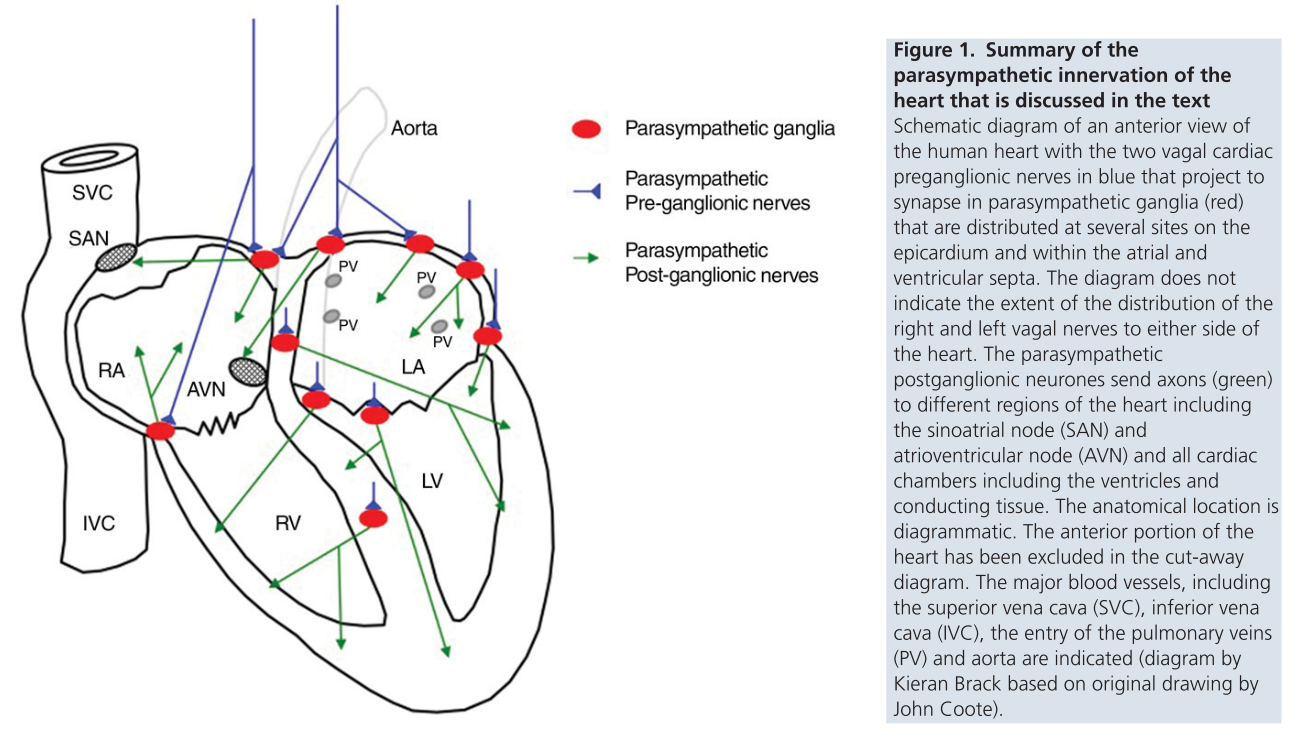
# History

1. VF first proposed as mechanism of sudden cardiac death
   1. 1889 first time that ventricular fibrillation proposed as mechanism for SCD (de Silva, 1989)
      1. prior to advent of ECG
      2. historically called *fatal syncope*, although still cardiac syncope still has significant independent mortality (Koene, Adkisson, & Benditt, 2017)
   2. occurred historically under Carl Ludwig in Leipzig, the home of the Ludwig Institute of physiology (training site of Fick, Pavlov, Kronecker)
      1. inventor of kymograph, the first method to record blood pressure
      2. applied electricity to the hearts of mammals inducing *cardiac tetany*
   3. previous names of ventricular fibrillation - delirium cordis, circus contraction, intervermiform movement
   4. First successful defibrillation of the human heart was in 1947 (Meyer, 1988)
   5. Ventricular tachycardia, as a pre-fibrillatory rhythm, requires low-energy for cardioversion, thus, can be reverted by the precordial thump.(Pennington, Taylor, & Lown, 1970)
      1. 

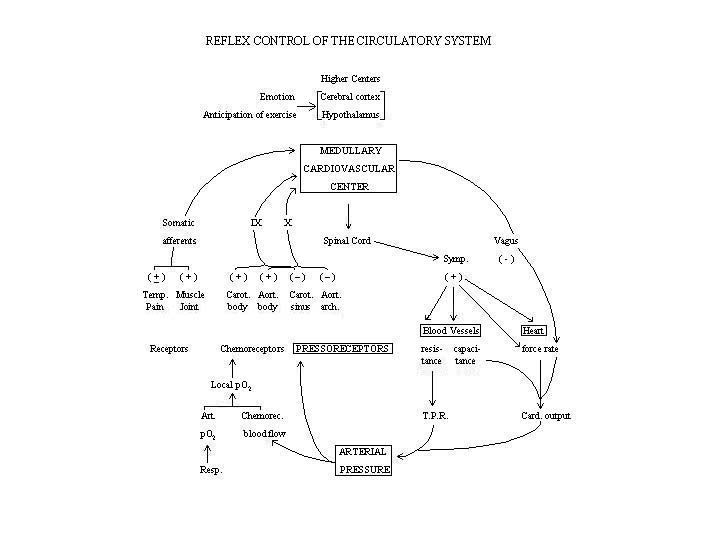
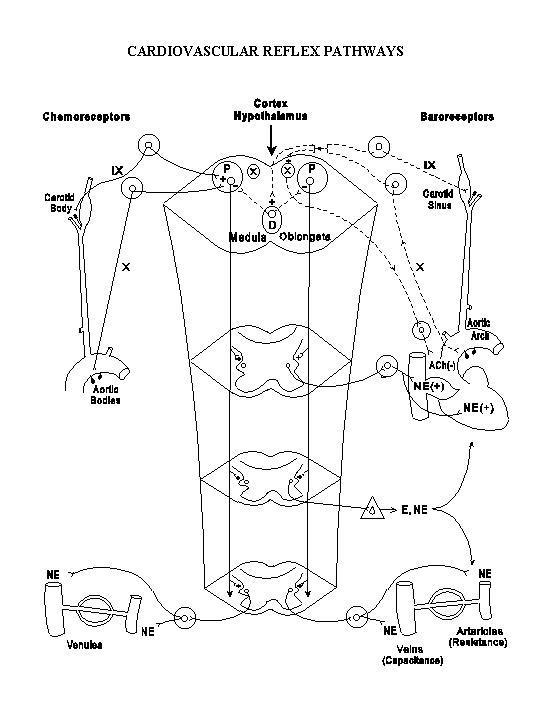
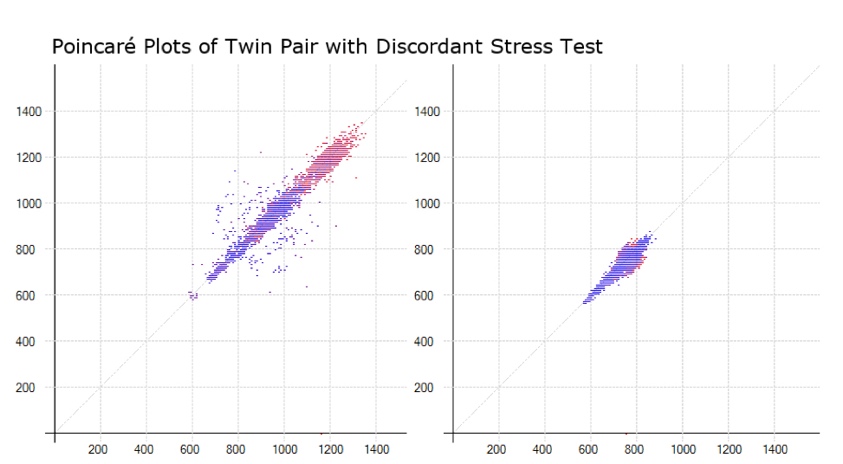
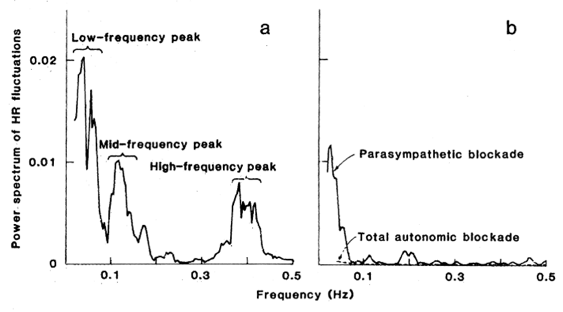
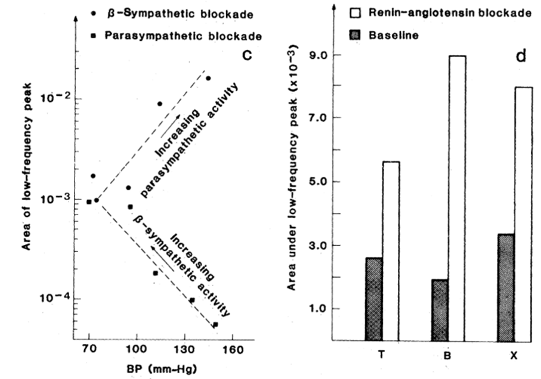
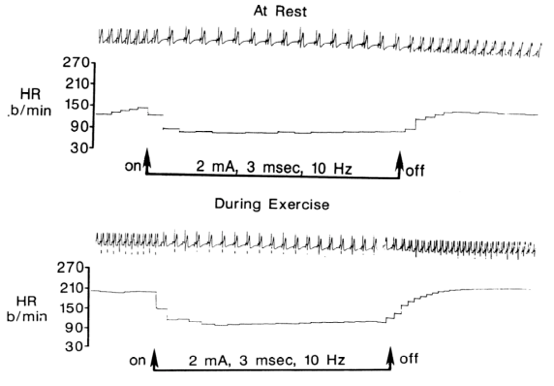
## Model of sudden cardiac death

1. Coronary care unit (Lown & Selzer, 1968)
   1. Bernie Lown proposed that a specialized unit will reduce mortality after myocardial ischemia
      1. 70-90% of post-MI have ventricular extrasystole
      2. Built on the premise of 1) quiet/restful rooms, 2) continuous cardiac monitoring, 3) cardiac nurses, 4) oriented around prophylaxis of arrhythmias
      3. Reduction in rate of mortality from >30% to <20%
2. Concept of susceptibility to ventricular fibrillation
   1. Sudden death is an electrical accident that is based on 4 premises (Lown, Verrier, & Rabinowitz, 1977)
      1. Mechanism of sudden death is ventricular fibrillation
      2. Electrical instability of the myocardium may long precede onset of catastrophic arrhythmia
      3. Ventricular premature beats may reflect electrical instability, which in turn may predispose the unstable heart to develop repetitive ventricular activity and subsequent fibrillation
      4. Transient risk factors induce electrical instability and increase cardiac susceptibility to ventricular fibrillation (thought from nervous activity)
   2. The autonomic nervous system, for example, affects/modulates risk for ventricular activity. (Lown et al., 1977) Vagal nerve activity is protective and increased threshold against developing VF.(Kolman, Verrier, & Lown, 1975)
      1. 
3. Substrate model (draw out model)
   1. Ventricular substrate is modified by factors such as ischemia
   2. Triggers, such as autonomic stimuli, then precipitate VT/VF

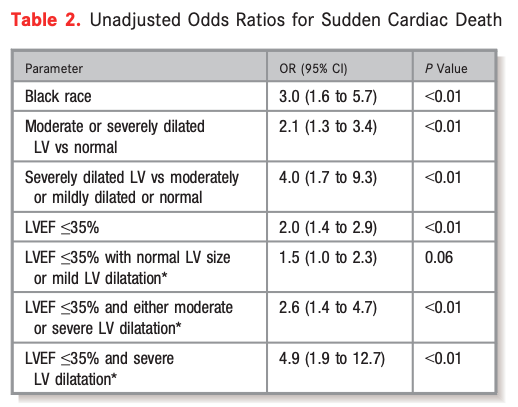
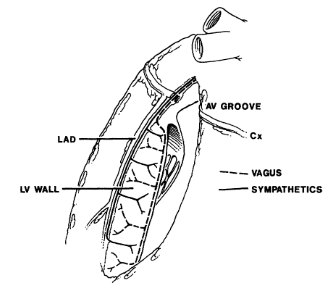
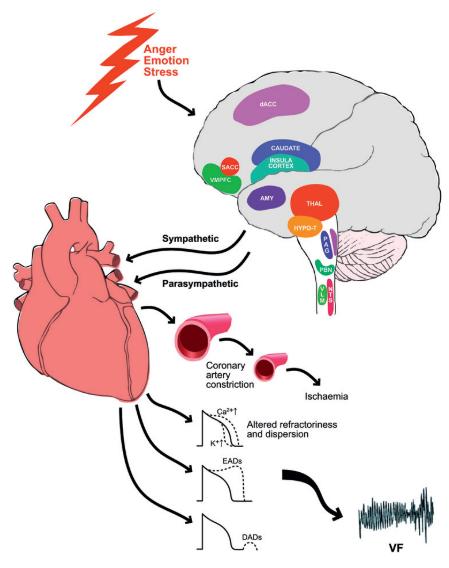
## Autonomic nervous system

1. Anatomy and neurocardiac axis
   1. Neurocardiac axis as described by Armour.(Armour, 2010) The anatomy is complex, but simplifies down to local ganglion plexus in cardiac fat pads (see echo).
      1. 
      2. 
   2. Complex model suggesting directionality of afferent and efferent sympathetic markers.(Davis & Natelson, 1993)
      1. 
2. Sympathetic tone can lead to increased risk of VF.
   1. Stimulation of the stellate ganglion in canine models had increased chance of causing ventricular fibrillation particularly after coronary occlusion.(Harris, Otero, & Bocage, 1971)
   2. Stellate ganglion thought to be carrying efferent sympathetic fibers. After stellate ganglionectomy, the VF threshold increased to 11% from 31% (compared to control VF rate).(Kliks, Burgess, & Abildskov, 1975)
   3. Effect is complicated however, as unilateral stellectomy may have compensatory contralateral activation, and then are agonized by vagal activity.(Schwartz, Verrier, & Lown, 1977)
3. Vagal tone can be protective.
   1. Vagal influence was not thought to be salutary independently, it only provided protection to VF threshold with concurrent increased sympathetic tone.(Kolman et al., 1975)
   2. Vagal nerve asks through muscarinic, nicotinic, and adrenergic signals, such as methacholine could raise ventricular vulnerable threshold, which could reduced with atropine.(Rabinowitz, Verrier, & Lown, 1976)
   3. Vagal activity is controversial, as sympathetic-independent nitrergic parasympathetic postganglionic nerves can independently provide ventricular protection and decrease SA-AV conduction.(Brack, Coote, & Ng, 2011; Brack, Patel, Coote, & Ng, 2007; Ng, Brack, & Coote, 2001)
      1. 
      2. Multiple types of cardiac vagal preganglionic neurons exist in the medulla in feline models, one affected by respiration and one that was not.(Daly & Kirkman, 1989)

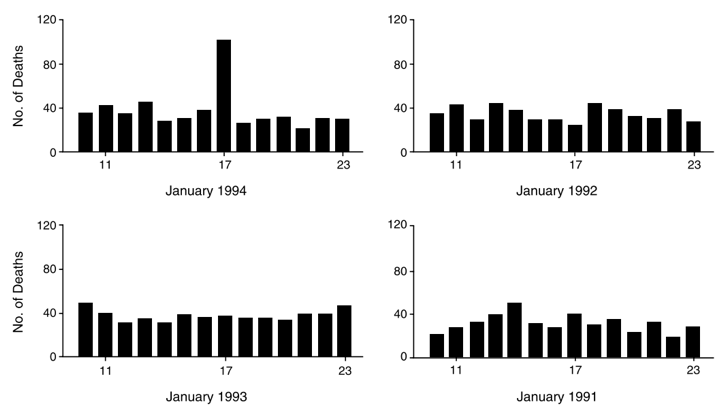
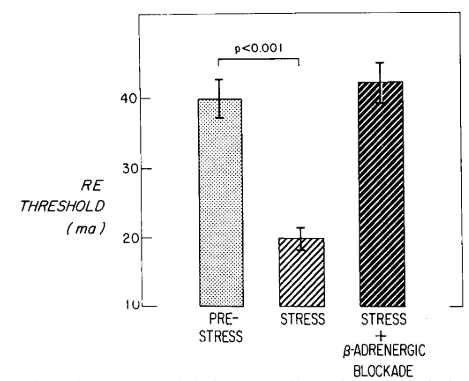
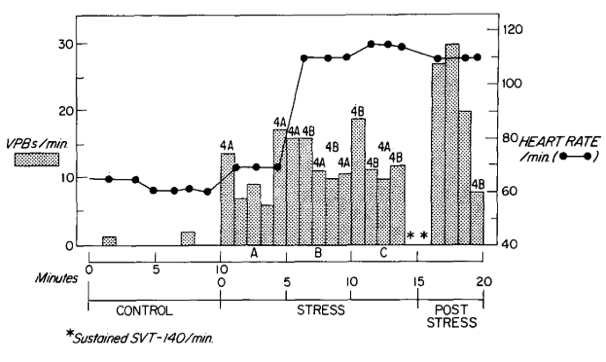
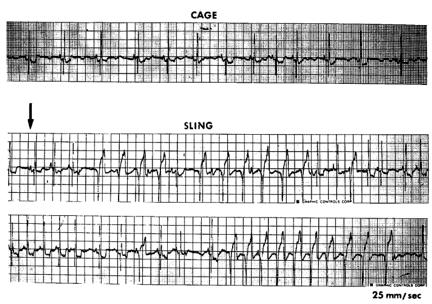
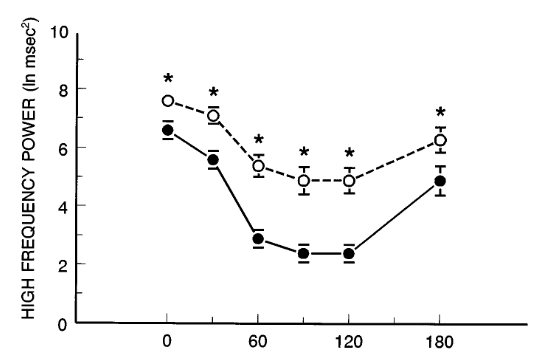
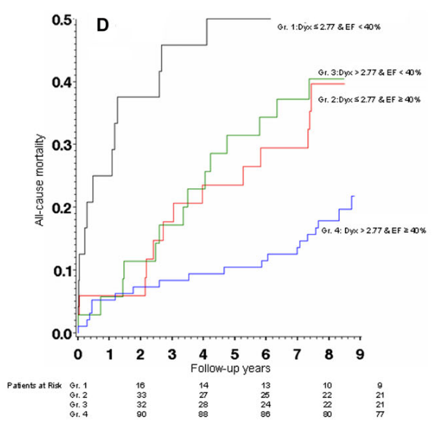
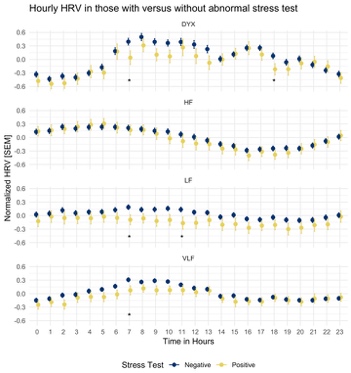
# Heart rate variability

1. Purpose of HRV
   1. The multiple factors that influence the cardiovascular system include many levels of reflex arches and firing within the autonomic nervous system.
   2. A final integration of dynamic autonomic tone is on the sinoatrial node, measured by HRV. This is a summation point for multiple levels of control, from environmental, positional, contextual elements to volume status, respiration, etc.
      1. 
      2. 
2. Measurement
   1. The measurement of HRV is mathematically complex and interesting. There are standard, geometric domains, but also non-linear and frequency. It is measured in RR or NN intervals (beat-to-beat), usually designated as sinus beats. Traditionally decreases in time measures, such as the SD of the NN interval, suggested worse prognosis.(Kleiger, Miller, Bigger, & Moss, 1987; Lombardi et al., 1987)
   2. Non-linear domain is novel, developed over last several years.(Tayel & AlSaba, 2015)
      1. Two Poincaré plots that represent one hour of ECG data at 7 AM between a twin pair discordant for myocardial stress perfusion abnormalities. Each point represents an RR interval (ms) on the x-axis plotted against the following RR interval (ms) on the y-axis over the course of the recording. The first twin (left) was negative for myocardial stress perfusion deficits (Dyx = 3.7), and the second twin (right) was positive for myocardial perfusion deficits (Dyx = 1.7).
      2. 
   3. Frequency domain measures are an attempt to study HRV in terms of physiological correlates, through power spectral analysis.(Akselrod et al., 1981) By using a Fourier transform, the series of RR intervals are decomposed and broken into bands, each corresponding to a physiological measure. HF occurs at ~0.4 Hz, which corresponds to respiratory rate.
      1. 
      2. 
      3. Very low frequency (VLF) is between 0.0033 and < 0.04 Hz; low frequency (LF) is between 0.04 and < 0.15 Hz; and high frequency (HF) is between 0.15 and < 0.40 Hz. These frequency bands integrate heart rate in response to physiologic stimuli, including influences of the renin-angiotensin-aldosterone system (VLF), baroreceptor activity (LF), and respiration (HF).
3. Responsiveness of vagal and sympathetic tone
   1. Measure the different components is quite useful, particularly in teasing apart the effects. This study uses a conscious canine model to demonstrate an important, summative concept of *accentuated antagonism*.(Stramba-Badiale et al., 1991) Each dog has had a vagal nerve stimulator implanted in the cervical region, and subsequently had this activated during exercise versus at rest. 1) Immediately there is a change in heart rate with stimulation, suggesting that vagal activity is very rapid in its effect, almost instantaneous. 2) The effect was over-proportional to the amount of sympathetic tone (e.g. at higher heart rates, a larger bradycardic response occurred).
      1. 
   2. The vagus and sympathetic system thus must communicate and interact, potentially at multiple levels.
4. Review of HRV and ANS
   1. HRV is final integration of ANS on the heart
   2. Vagal tone is sudden, sympathetic is slow
   3. Altered or low HRV tends to suggest poor prognosis, and may even be predictive.

## Ventricular substrate

1. Differential innervation of the heart
   1. The inferior wall of the left ventricle has a higher proportion of vagal afferent neurons, such that inferior ischemia, usually from the RCA system, leads to a cardioinhibitory pattern and subsequent sinus bradycardia.(Walker, Thames, Abboud, Mark, & Kloppenstein, 1978)
   2. In humans, imaging shows a consistent pattern of increased vagal innervation of the inferior wall, based on MIBG uptake in the myocardium.(Morozumi et al., 1997)
2. Ventricular size
   1. Historically, >4 cm of ventricle was needed to sustain VF.(de Silva, 1989) This is consistent with current research that shows a higher left ventricular volume/mass increases susceptibility to VF.(Aras, Faye, Cathey, & Efimov, 2018; Shenasa & Shenasa, 2017)
   2. LVIDD increases the risk of SCD independently of reduced EF.(Narayanan et al., 2014)
      1. ****
3. Ischemia
   1. The depth of ischemia is important. Transmural infraction leads to sympathetic denervation, unlike subendocardial ischemia, which may only damage vagal efferent nerves (as seen in figure).(Herre et al., 1988; Zipes, 1990)
      1. ****
   2. Response to ischemia can be both denervation as well as hyperinnervation, which leads to tissue that has heterogenous sympathetic fibers, leading to arrhythmogenesis.(Huang, Boyle, & Vaseghi, 2017) The location of ischemia is also important, as measuring postganglionic activity shows differences in activity depending on whether it serves ischemic versus nonischemic territory.(Neely & Hageman, 1990)
4. Review substrate model
   1. Simplified model suggesting how ANS affects cardiac refractoriness and repolarization.(P Taggart, Critchley, & Lambiase, 2011)
      1. 

## Triggering sudden death

1. Precipitating events
   1. Anecdotes of events of threat, grief, arousal, mourning, personal danger, reunion precede sudden death.(Engel, 1971)
      1. After the Northridge earthquake in 1994, there was an increase in number of SCD, even after accounting for trauma or physical exertion.(Leor, Poole, & Kloner, 1996)
         1. 
      2. In an industrial plant in Rochester, NY, there were 26 reported cases of sudden death. Interviews with family noted that these individuals had been depressed over the past several weeks, and the events happened in the setting of acute arousal, either through increased work, anxiety, or anger.(Greene, Goldstein, & Moss, 1972)
      3. Increasing stress has been shown to precede SCD,(Rahe, Bennett, Romo, Siltanen, & Arthur, 1973) and when measured in patients with ICD, VT and VF showed a similar pattern.(Lampert et al., 2002; Peter Taggart, Boyett, Logantha, & Lambiase, 2011)
   2. The events also follow a circadian rhythm. Peak events of MACE occur from 6 AM to 10 AM, followed by a secondary peak of events from 6 PM to 8 PM.(Boudreau, Dumont, Kin, Walker, & Boivin, 2011; Muller, 1999; Portaluppi et al., 2012)
   3. Increasing the frequency of VT and VF after induction of stressful situations.(Lown, Verrier, & Corbalan, 1973; Lown et al., 1977; Verrier, Calvert, & Lown, 1975)
      1. 
      2. 
      3. 
2. Autonomic risk
   1. In canine model, those at risk for VF after stress/coronary occlusion had decreased HRV during testing, suggesting an independent/additional risk factor.(Houle & Billman, 1999)
      1. 
   2. Increased mortality with autonomic dysfunction seen in multiple studies.(Bauer, 2017; De Ferrari et al., 2007; Jørgensen et al., 2016; La Rovere, Bigger, Marcus, Mortara, & Schwartz, 1998)
      1. 
   3. Potential explanation of autonomic risk is microvascular ischemia, changes in resistance vessels, although its not certain if epicardial vessels could be obstructed either.
      1. 

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