Bioeng 6460
Electrophysiology and Bioelectricity

Fundamentals of Arrhythmias

(Part 1)

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Overview

- Motivation for studying arrhythmia/epidemiological data
- The origin of rhythm and synchronicity
- Arrhythmia mechanism classification
- Abnormal impulse formation
  - Automatic (Normal and abnormal mechanisms)
  - Triggered (Early afterdepolarizations (EADs) and Late afterdepolarizations (DADs)
- Bioengineering approaches to biological pacamakers

Motivation for Studying Arrhythmia?

Mortality data

Mortality experience in 2007

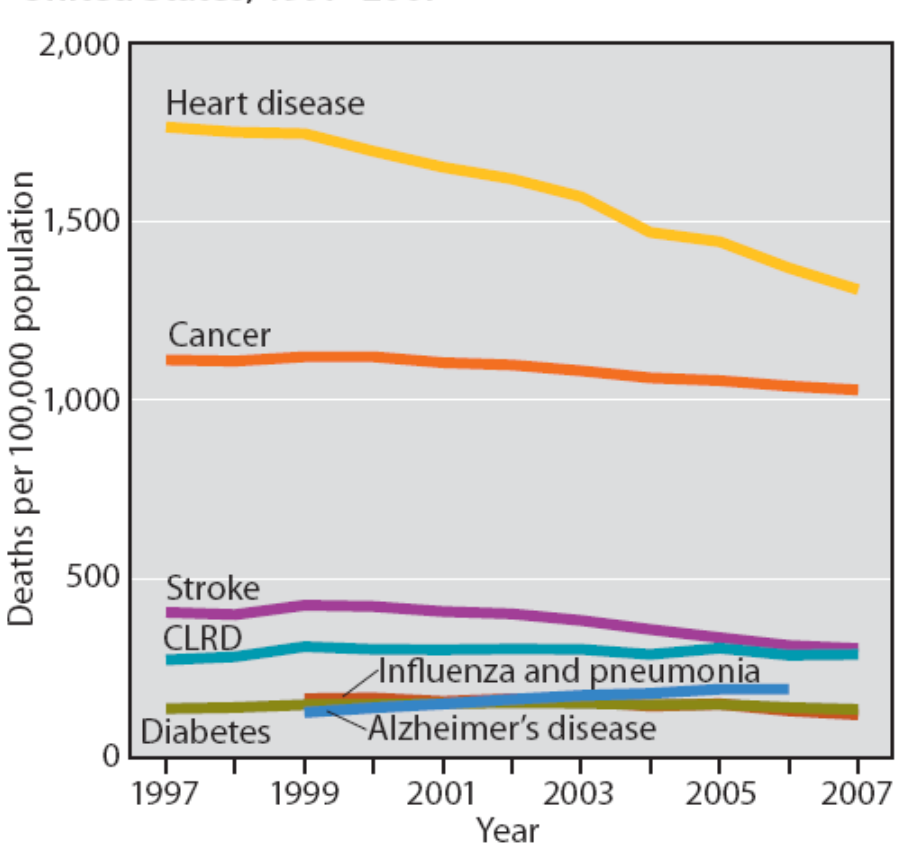
- In 2007, a total of 2,423,712 resident deaths were registered in the United States.
- The age-adjusted death rate, which takes the aging of the population into account, was 760.2 deaths per 100,000 U.S. standard population.
- Life expectancy at birth was 77.9 years.
- The 15 leading causes of death in 2007 were:

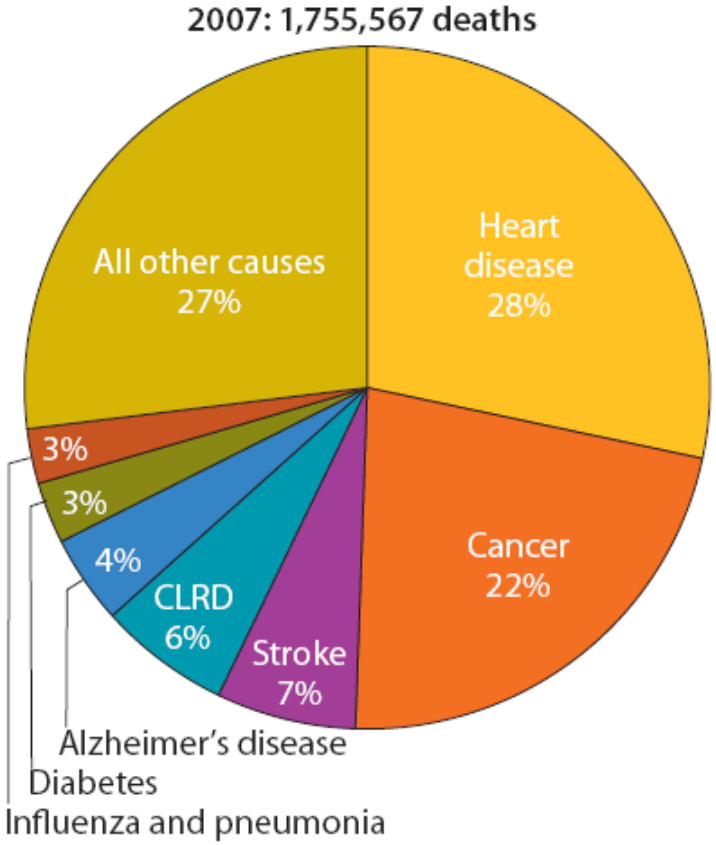
1. Diseases of heart (heart disease)
2. Malignant neoplasms (cancer)
3. Cerebrovascular diseases (stroke)
4. Chronic lower respiratory diseases
5. Accidents (unintentional injuries)
6. Alzheimer's disease
7. Diabetes mellitus (diabetes)
8. Influenza and pneumonia
9. Nephritis, nephrotic syndrome and nephrosis (kidney disease)
10. Septicemia
11. Intentional self-harm (suicide)
12. Chronic liver disease and cirrhosis
13. Essential hypertension and hypertensive renal disease (hypertension)
14. Parkinson's disease
15. Assault (homicide)

http://www.cdc.gov/nchs/fastats/heart.htm (Centers for Disease Control and Prevention)

Mortality data

Figure 31. Death rates for leading causes of death among persons 65 years of age and over: United States, 1997–2007



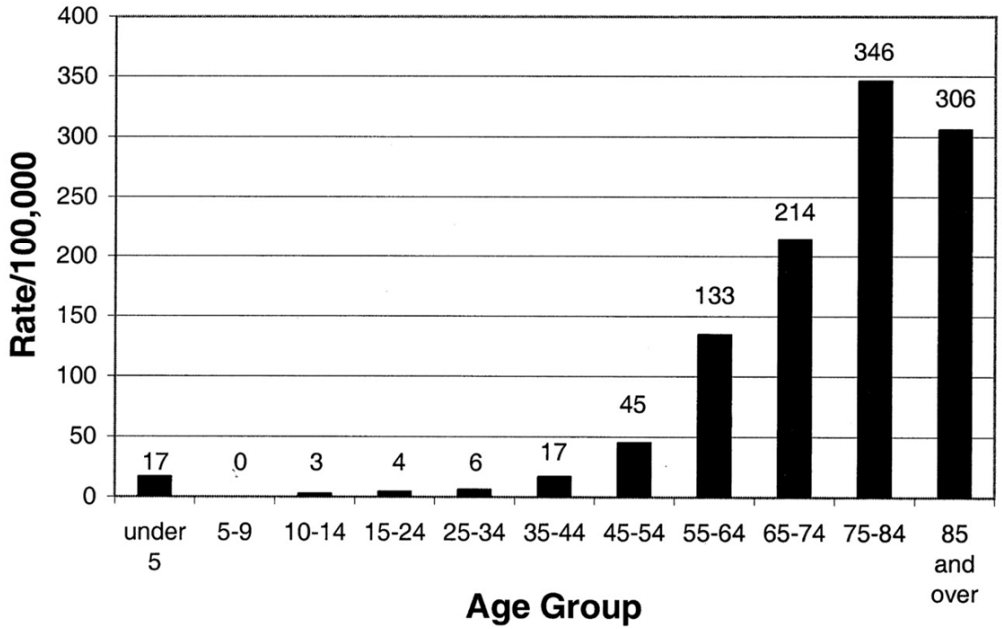


NOTE: CLRD is chronic lower respiratory diseases.
See data table for Figure 31.

SOURCE: CDC/NCHS, National Vital Statistics System.

Epidemiology of arrhythmias/sudden cardiac death

Age-based annual incidence of sudden cardiac death among residents of Multnomah County, Oregon (population 660,486)



Chugh et al. Prog Cardiovasc Dis 2008

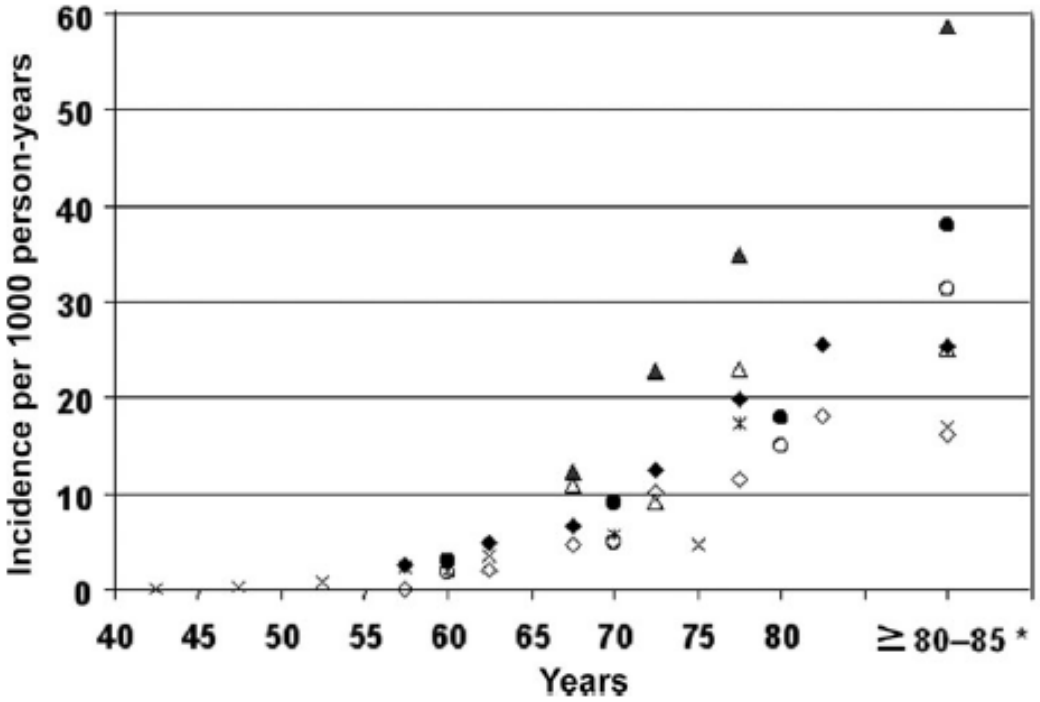
- The current annual incidence of sudden cardiac death in the US is likely to be in the range of 180,000-250,000 /year (Chugh et al.)
- In the overwhelming majority of cases sudden cardiac death results from a fatal cardiac arrhythmia, either VT/VF or severe bradycardia/pulseless electrical activity (Myerburg Castellanos 1997, Zipes Wellens 1998)
- There are two well established peaks in the age-related prevalence of sudden cardiac death, one during infancy representing the sudden infant death syndrome and the second in the geriatric age group (75-85 yrs)

Epidemiology of arrhythmias/atrial fibrillation

- Most common arrhythmia: 5% in > 65 years of age, 9% > 80 years
- Most common causes: ischemic heart disease, hypertension, mitral stenosis, congestive heart failure
- Presence of AF doubles mortality, increases risk of stroke by factor 2-7
- Once a heart is in AF, it becomes harder and harder to stop ("AF begets AF")

Epidemiology of arrhythmias/atrial fibrillation

Age specific incidence of AF



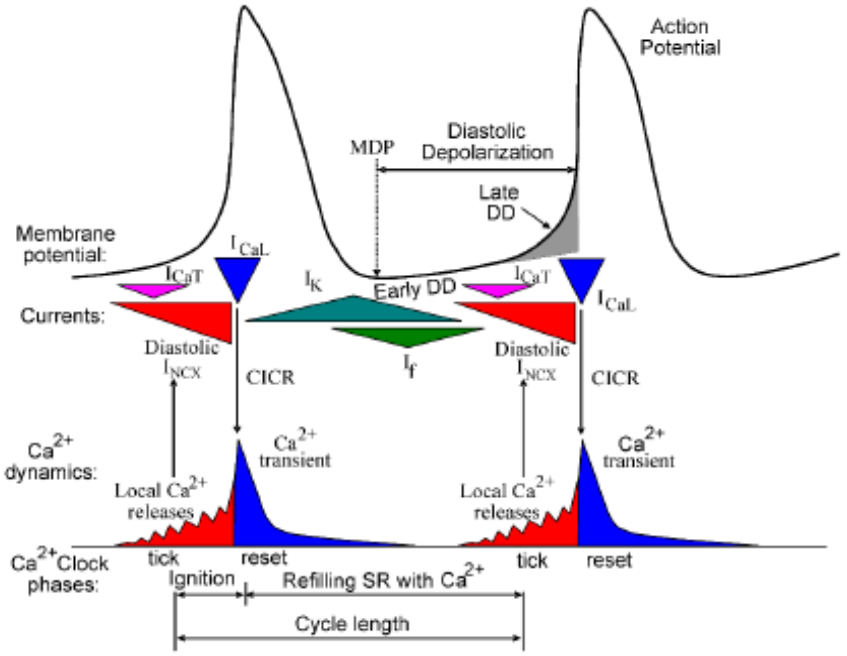
Additionally, bear in mind 1) the increase in aging population in the US/Europe/Japan as well as the higher life expectancy in 'developing world' countries; 2) epidemic diseases such as type 2 diabetes are also associated to an increase propensity for AF (Huxley et al. Circulation 2011)

Boriani et al. Eur Heart J 2006

The origin of rhythm/biological clocks

Automaticity: The ability of specialized cardiac cells such as normal sino-atrial node (SAN) cells, cells in some parts of the atria, atrioventricular junctional region cells, and in the His-Purkinje system myocytes to initiate ***spontaneous*** action potentials.

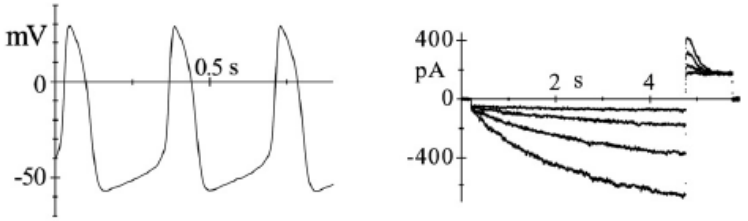
Mechanism: Not a single ionic mechanism is responsible for pacemaking. The combination of 1) the decay of outward K^+ current, 2) an inward depolarizing current (I_f), which becomes more pronounced at more negative membrane diastolic potential (MDP), and 3) a Ca^{2+} current in the later phases elicits spontaneous depolarization of SAN cells. I_{K1} rectification determines the voltage sensitivity to changes in membrane current via its effect on membrane resistance.



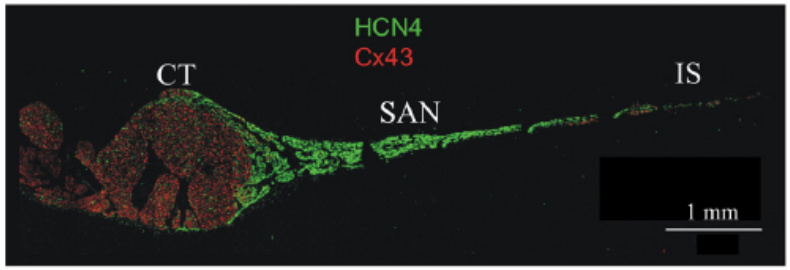
Ca^{2+} Clock: An additional intracellular mechanism involved in SAN cell activation and rate regulation which involves the spontaneous release of Ca^{2+} from the SR an the interaction of this phenomenon with membrane potential via I_{NCX} amongst others.

Lakatta et al. Circ Res 2010

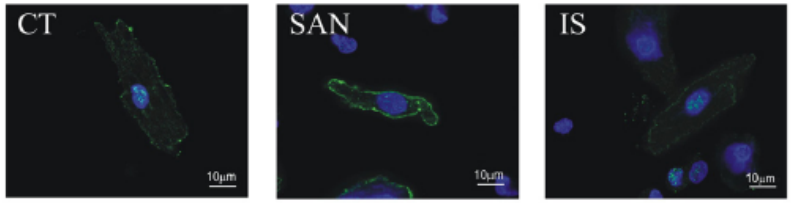
The origin of rhythm/biological clocks



The I_f current, A.K.A. the 'funny current', plays a major role in initiating the diastolic depolarization of SAN cells.



I_f is activated on hyperpolarization at voltages below about -40/-45 mV and is inward in its activation range, its reversal potential being about -10/-20 mV.



I_f increases during perfusion with adrenaline, and it is present in the SAN, in the atrio-ventricular node (AVN), and in Purkinje fibers.

Molecular identity of I_f: Forms part of a group of channels known as the hyperpolarization-activated cyclic nucleotide (HCN) family, comprised by four members (HCN1 to HCN4), and which are part of a superfamily of voltage-gated potassium (Kv) channels, with which they share similar characteristics. In the SAN tissues of humans and lower mammals, the predominant molecular constituent of I_f is the HCN4 isoform.

DiFrancesco Circ Res 2010

Limit cycle oscillations

Poincare oscillator

$$d\phi/dt = 1$$
$$dr/dt = kr(1 - r)$$

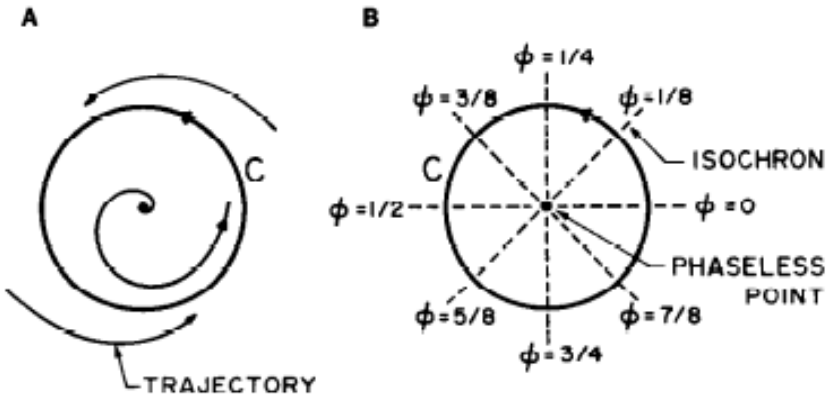


FIG. 3. *A*: schematic representation of phase plane of limit cycle oscillator. All points, except for singular phaseless point, attract to limit cycle (C) as $t \to \infty$. *B*: for simple model in *Eq. 4*, isochrons (see text, *dashed lines* in *right-hand panel*) are straight lines that approach arbitrarily closely to singular point. For *Eq. 4* limit cycle is circle with radius = 1.

Limit cycle oscillators are a particular type of non-linear mathematical oscillators that display periodic solutions that are attracting as time approaches infinity, as long as the initial conditions are close to the cycle.

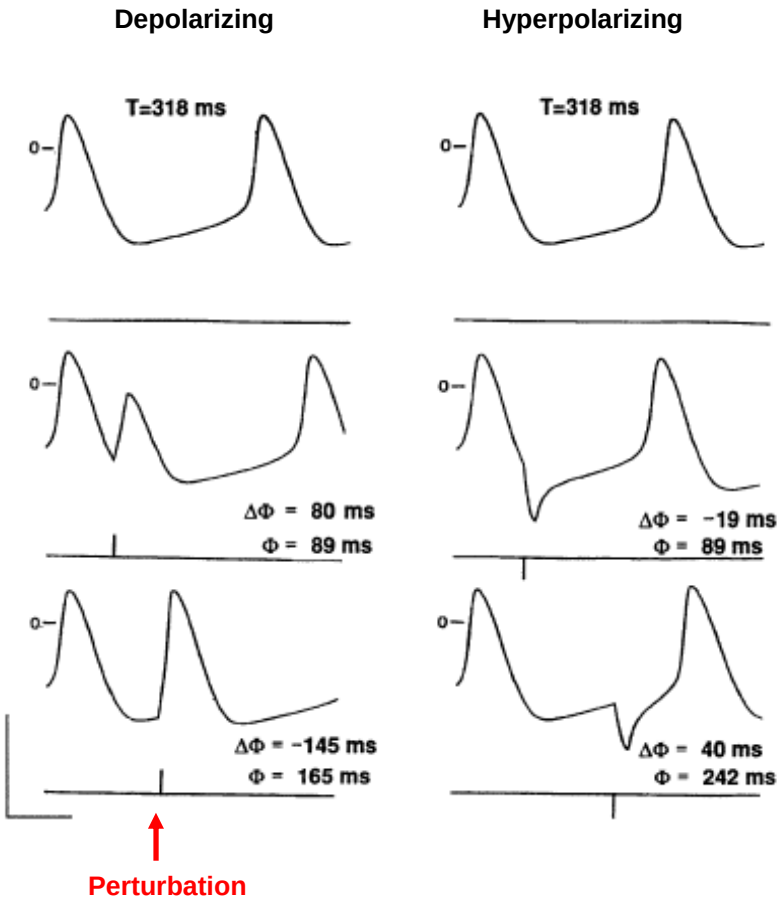
The Poincare oscillator is a simple type of limit cycle oscillator and can be described with two variables.

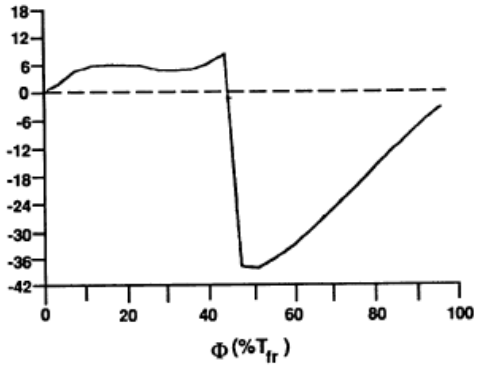
The key point is that many biological oscillators including pacemaker oscillations display physical properties which can be predicted from the solutions of the limit cycle oscillators, including the Poincare oscillator.

Glass and Winfree AJP 1984

Glass and Shrier. Theory of heart. Springer-Verlag, 1991

Entrainment/resetting the biological clock

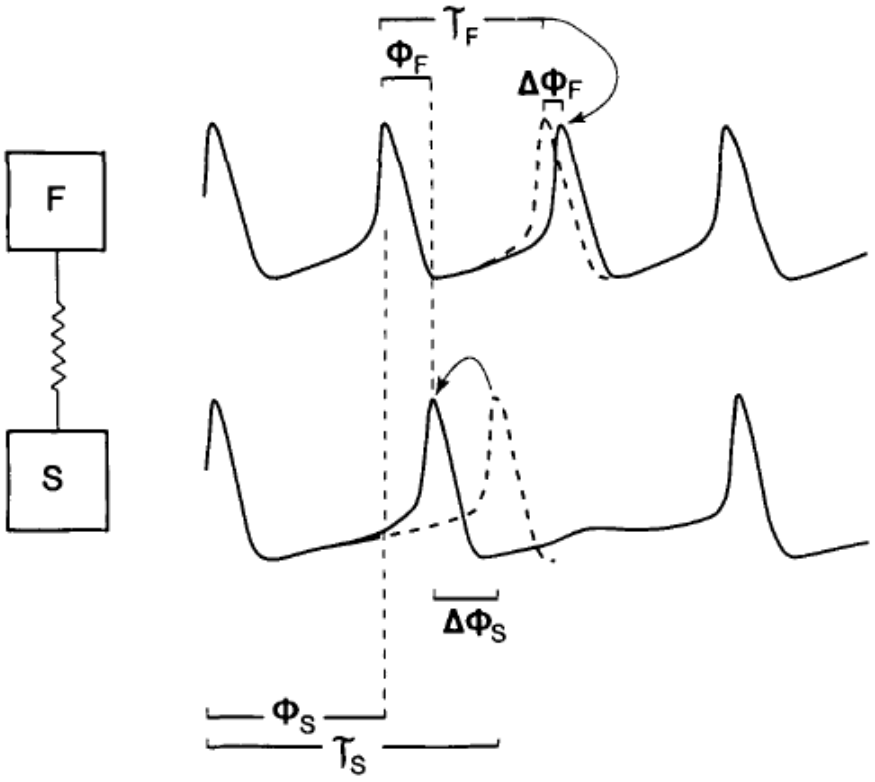




Small perturbations (depolarizing or hyperpolarizing) of biological pacemakers induce predictable shifts in the phase of the oscillation depending on the timing of the event. These shifts may be positive or negative, i.e. advance or delay of the phase respectively, and are clearly visualized when presented in the form of a phase response curve.

Anumonwo et al Circ Res 1991

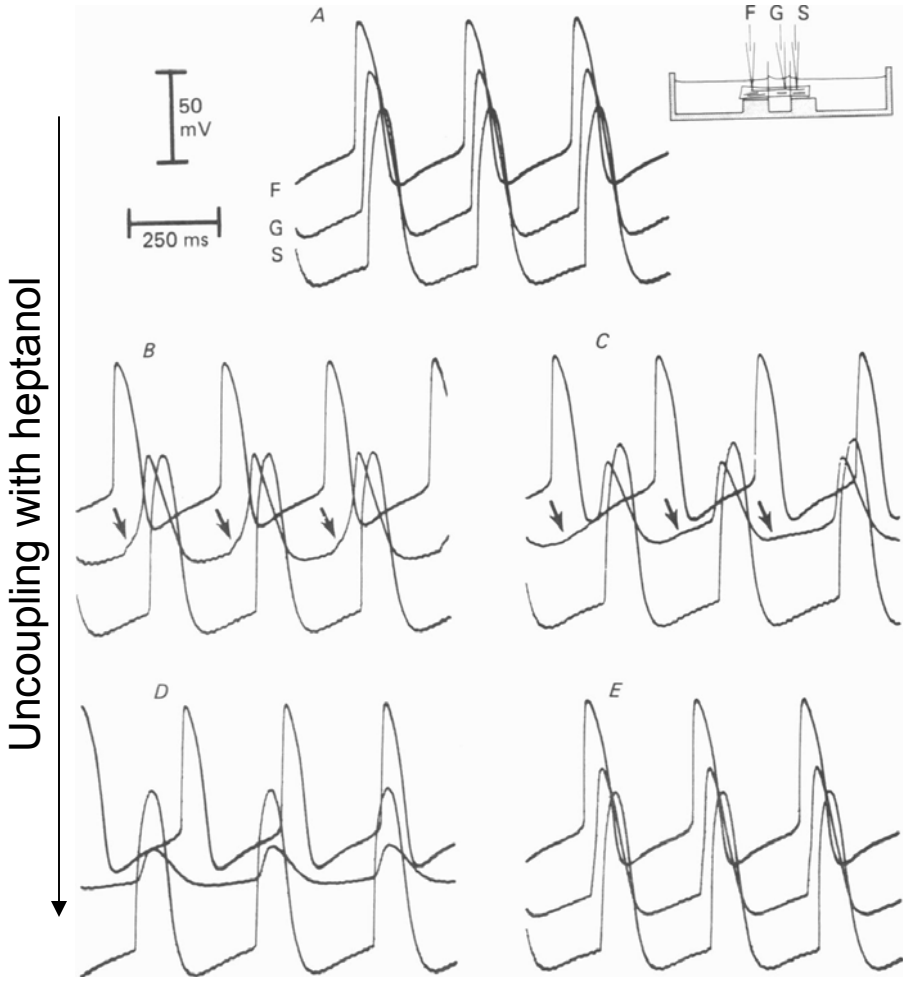
Mutual Entrainment

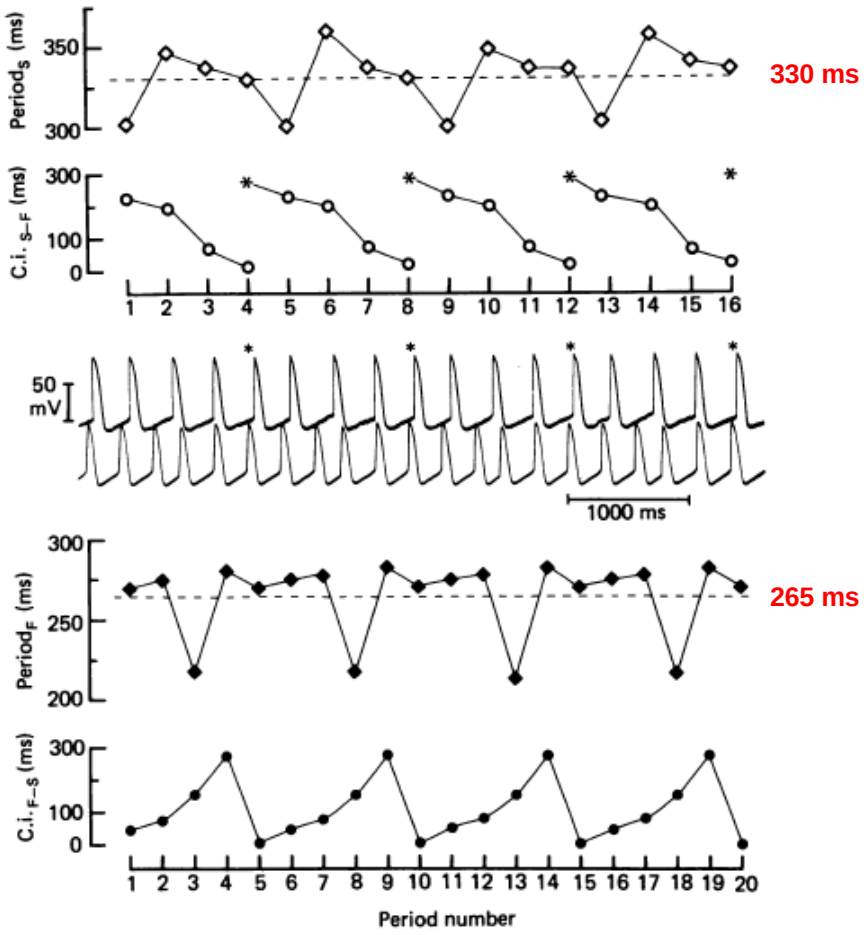


The interaction between two coupled oscillators (with different intrinsic frequency F 'fast' and S 'slow') can be thought of as a problem of ***mutual entrainment***. For example, a depolarizing pulse from the fast oscillator F interacts with the slow oscillator and resets its phase by advancing the phase of the slow oscillator S by an amount ΔΦs. Conversely, the pulse generated by the slow oscillator then interacts with the fast oscillator and resets its phase by delaying the phase of the fast oscillator F by an amount ΔΦf. The interaction between the two oscillators may be mediated as shown in the next slide by electrotonic coupling of the myocytes.

Michaels et al Circ Res 1986

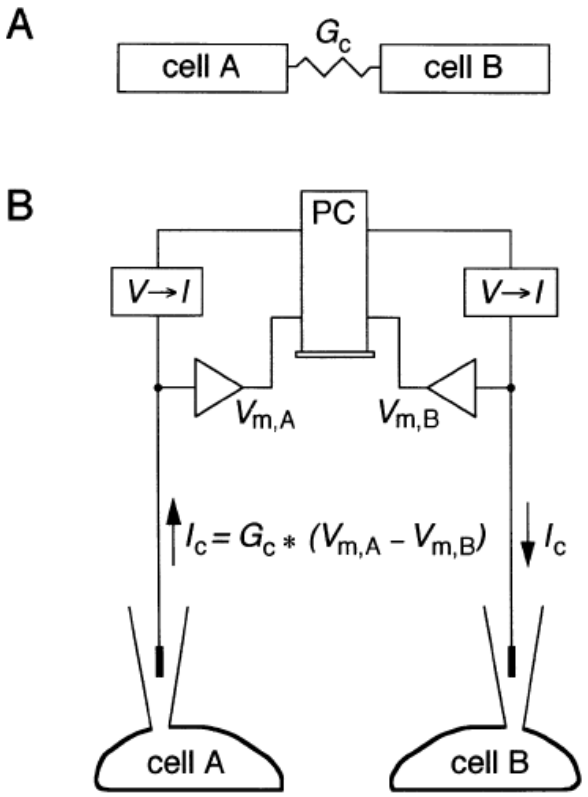
Synchronization of SAN cells





Jalife J Physiol 1984

Synchronization of SAN cells



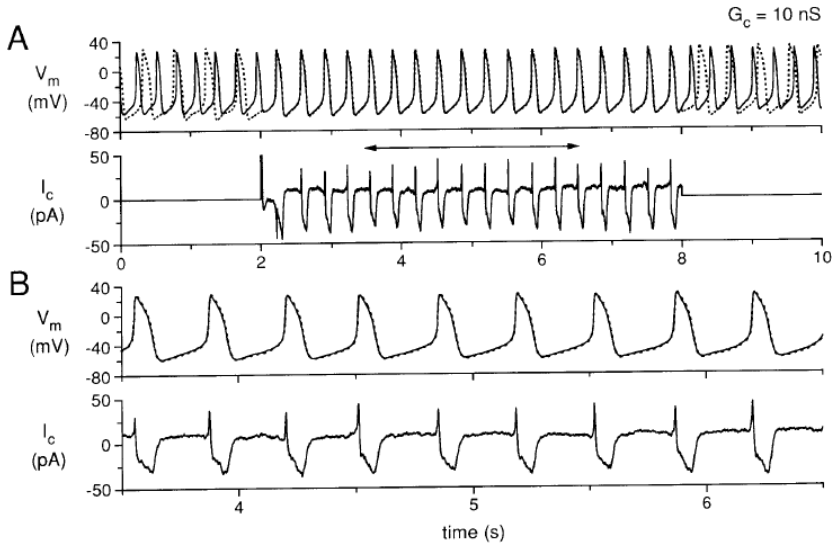
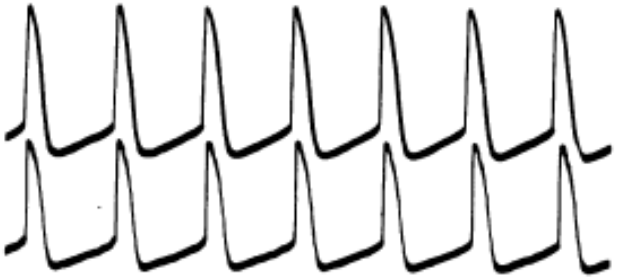


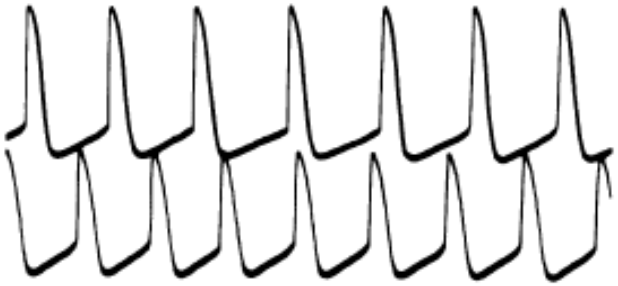
FIGURE 5. Simultaneous recording for 10 s of two isolated sinoatrial node cells, with the cells uncoupled during the first and last 2 s and coupled with a coupling conductance of 10 nS during the central 6 s. (*A*) Membrane potential (V_m) of cell A (*solid line*) and cell B (*dotted line*), and coupling current (I_c). (*B*) Data in *A* replotted for the time period indicated by the horizontal two headed arrow in *A*. Data from experiment 950803-2 (see Tables).

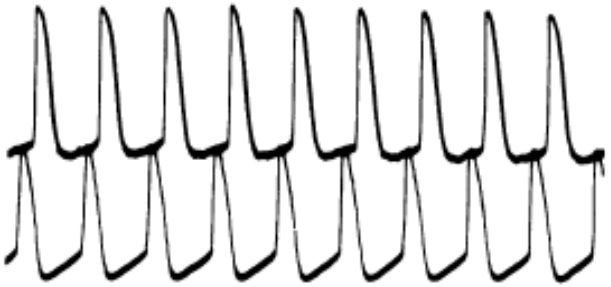
Result: When coupling conductance between the independent oscillators is high enough, frequency and waveform entrainment can be achieved.

Verheijck et al J Gen Physiol 1998

Group work







1) Identify the entrained trace pairs. Describe the differences between the entrained trace pairs and a plausible mechanism for the difference.

2) In the non-entrained trace pair which is the ‘fast’ pacemaker

Classification of arrhythmogenic mechanisms

- Abnormal Impulse Formation (Class 1)
  - Automatic
    - Normal automatic mechanisms
    - Abnormal automatic mechanisms
  - Triggered
    - Early afterdepolarizations (EADs)
    - Late afterdepolarizations (DADs)
- Abnormal impulse conduction (Class 2)

Useful definitions

Primary pacemakers: Cells from the sino-atrial node exhibiting normal automaticity. These cells are responsible for initiating the heart beat during normal function.

Latent (subsidiary) pacemakers: Non sino-atrial node cells which are capable of automatic activation. Examples include cells from the atrio-ventricular (AV) junction, some fibers/cells at the pulmonary veins, and cells from the His-Purkinje system amongst others.

Sino-atrial node

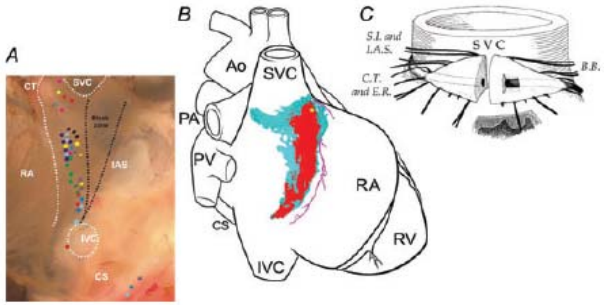


Figure 2. The sino-atrial node
A, position of the leading pacemaker site (coloured symbols) in the right atrium in 14 experiments superimposed on a photograph of one right atrial preparation. Black dotted lines show borders of block zone (a region of conduction block). From Fedorov *et al.* (2006) with permission. *B*, model of the rabbit sino-atrial node superimposed on a schematic diagram of the heart (dorsal view). Red, central sino-atrial node cells; blue, peripheral sino-atrial node tissue. From Dobrzynski *et al.* (2005). *C*, drawing of the human sino-atrial node. Purkinje tracts are shown exiting the sino-atrial node; these tracts (together with 'internodal pathways', which are shown in textbooks) are no longer thought to exist. From James (1961) with permission. Abbreviations: Ao, aorta; BB, Bachmann's bundle; CS, coronary sinus; CT, crista terminalis; ER, Eustachian ridge; IAS, interatrial septum; IVC, inferior vena cava; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SI, sinus intercavarum; and SVC, superior vena cava.

Atrio-ventricular node

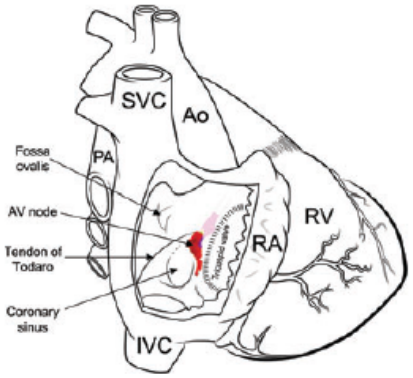


Figure 3. Model of the rabbit atrioventricular node superimposed on a schematic diagram of the heart (dorsal view)
A window has been cut in the right atrium to view the atrioventricular node. Abbreviations: Ao, aorta; IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava. From Li *et al.* (2008).

His-Purkinje system

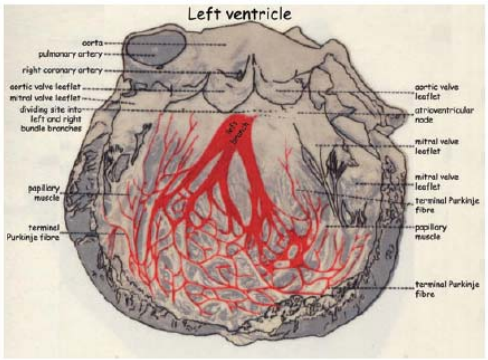
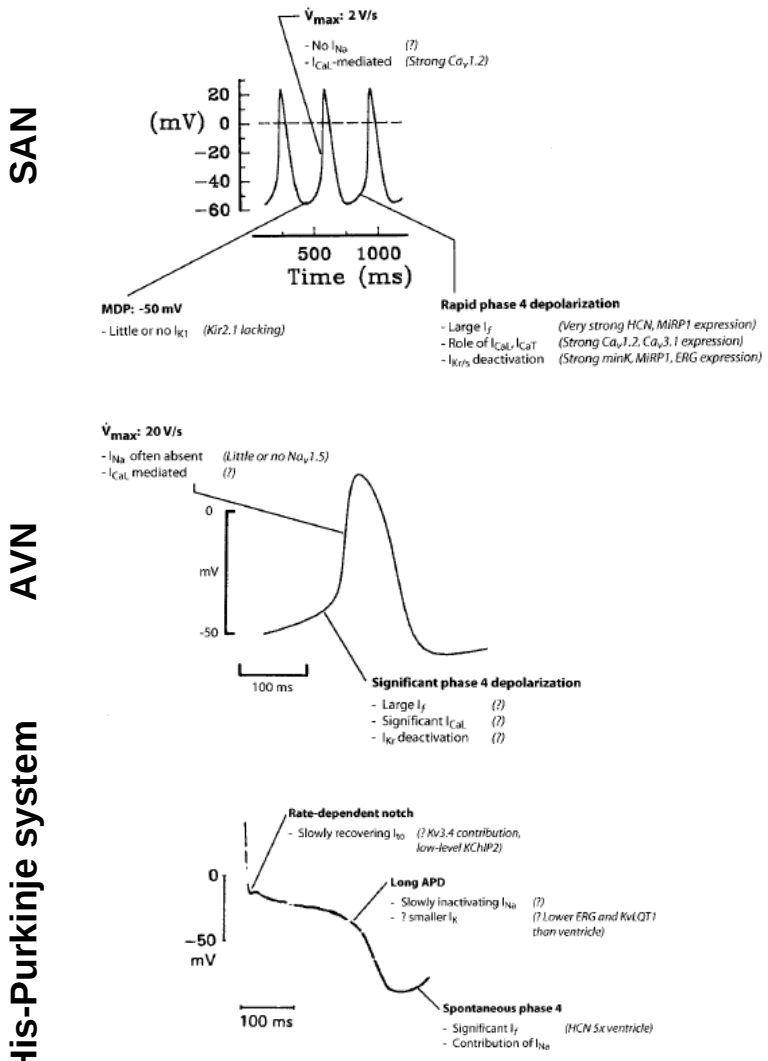


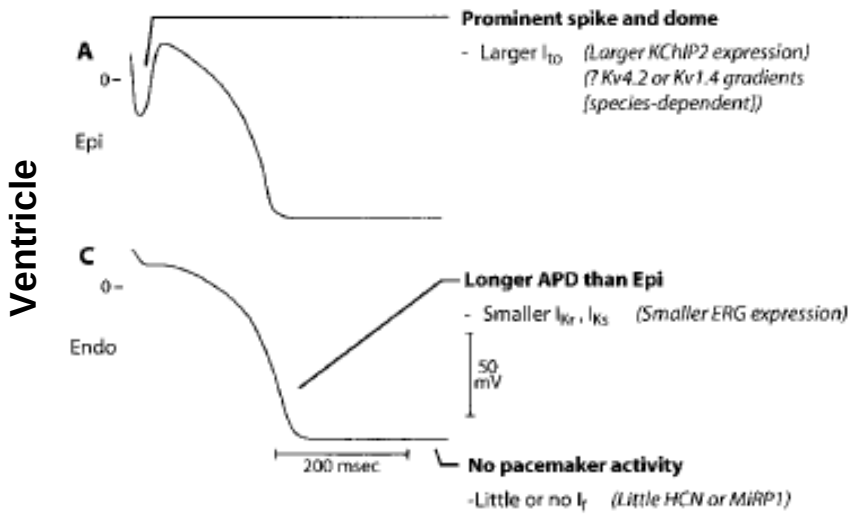
Figure 5. The His–Purkinje system in the human left ventricle
Modified from Tawara (2000) with permission.

Boyett Exp Physiol 2009

Reminder



Reminder: The electrical function of each particular specialized tissue involved in the cardiac excitation cycle is determined by the shape of the action potential (AP). The AP of each specialized tissue is in turn determined by the differential distribution of specialized cardiac ion channels which through their coordinated response to changes in transmembrane potential elicit the AP.



Schram et al. Circ Res 2002

Useful definitions II

Overdrive stimulation: External imposition of an activation rate faster than the 'intrinsic/spontaneous' rate of an automatic cell (cardiac pacemaker).

In the normal human heart cells from the AV junction and from the Purkinje system activate around 40-60 bpm and 20-40 bpm, respectively. In normal conditions these cell types are overdrive paced by excitation generated in the SA nodal cells whose normal intrinsic rate of firing is 60-100 bpm.

Overdrive suppression: During a period of overdrive stimulation the slope of phase 4 depolarization decreases, thus leading to a decrease in the firing rate upon cessation of the overdrive stimulus. The total period and frequency of the overdrive stimulus determine the degree of overdrive stimulation.

Overdrive suppression (Effect of time)

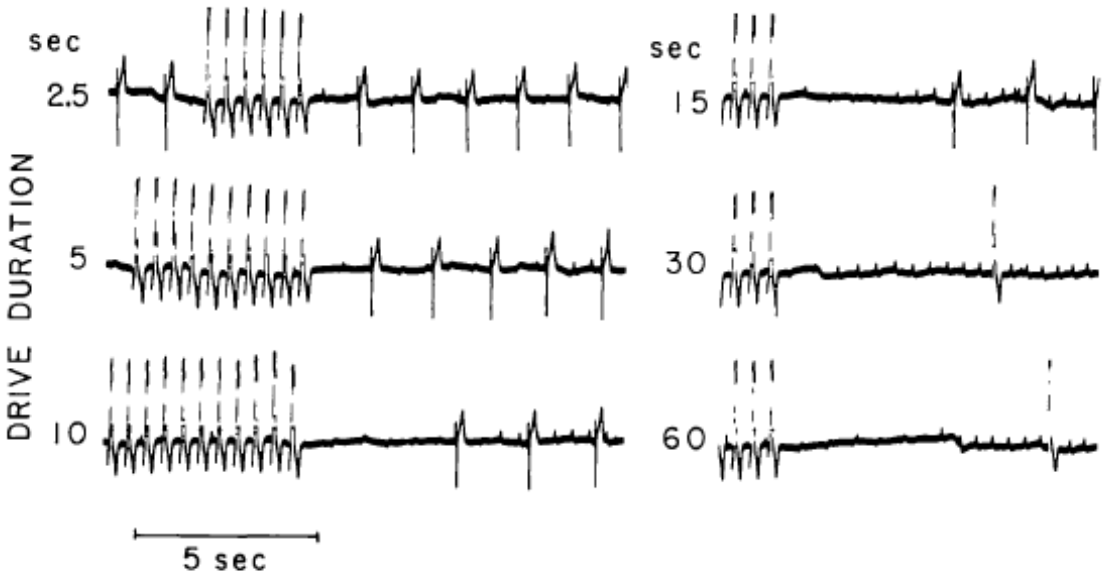


FIGURE 6

Effect of ventricular driving at a constant rate for different periods of time on the duration of subsequent asystole. The ventricular driving rate was 120/min; the QRS of the driven beats is positive. The duration of the period of drive is indicated in seconds by the numbers at the beginning of each trace. Only the last driven beats are shown for driving periods of 10 sec or more.

Result: Overdrive stimulation of increasing duration induces an increasing degree of suppression of automatic activity.

Vassalle et al. Circ Res 1967

Overdrive suppression (Effect of rate)

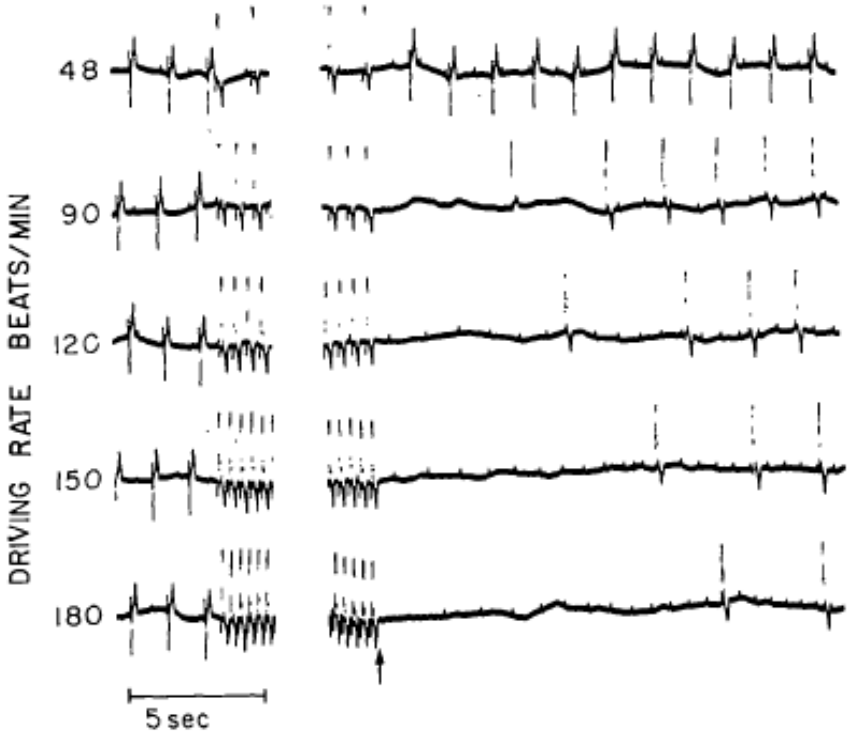


FIGURE 4

Unaltered duration of asystole after administration of neostigmine following ventricular overdrive for 60 sec in the same animal as in Figure 3. The explanation of the numbers and of the arrow is the same as in Figure 3.

Result: Overdrive stimulation of increasing driving rate induces increasing degrees of suppression of automatic activity.

Vassalle et al. Circ Res 1967

Overdrive suppression (Mechanisms)

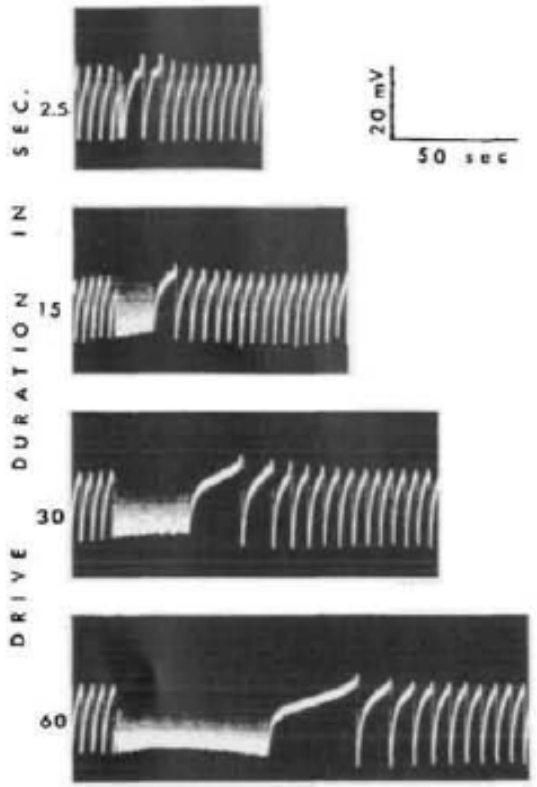


FIGURE 1

Effect of driving a spontaneously active preparation for different periods of time. Only the lower part of the action potentials is shown. The beginning of the upstroke is not seen. The final part of phase 3 repolarization is seen as a vertical thin line, much as those during overdrive. The trace is thicker during diastolic depolarization. $[K]_o = 2.7$ *mM.*

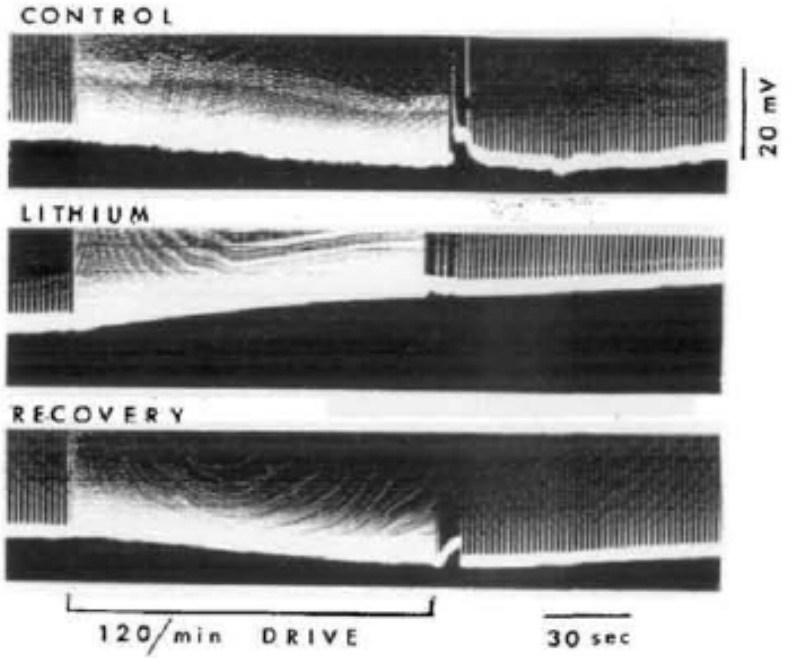


FIGURE 7

Substitution of sodium with lithium and changes in membrane potential with overdrive. $[K]_o = 5.4$ *mM. The shift in the trace immediately after the control overdrive period (top strip) is an artifact.*

Mechanism: When latent pacemakers are driven at a faster rate than their own intrinsic automatic rate, their intracellular sodium concentration is increased to a higher steady state level than would be the case during spontaneous firing. This results in an enhanced activity of the Na+/K+ pump in the sarcolemma. Because this pump moves three Na+ ions out of the cell against two K+ ions into the cell, it generates an outward (hyperpolarizing) current which counteracts the inward current responsible for spontaneous diastolic depolarization.

Vassalle et al. Circ Res 1970

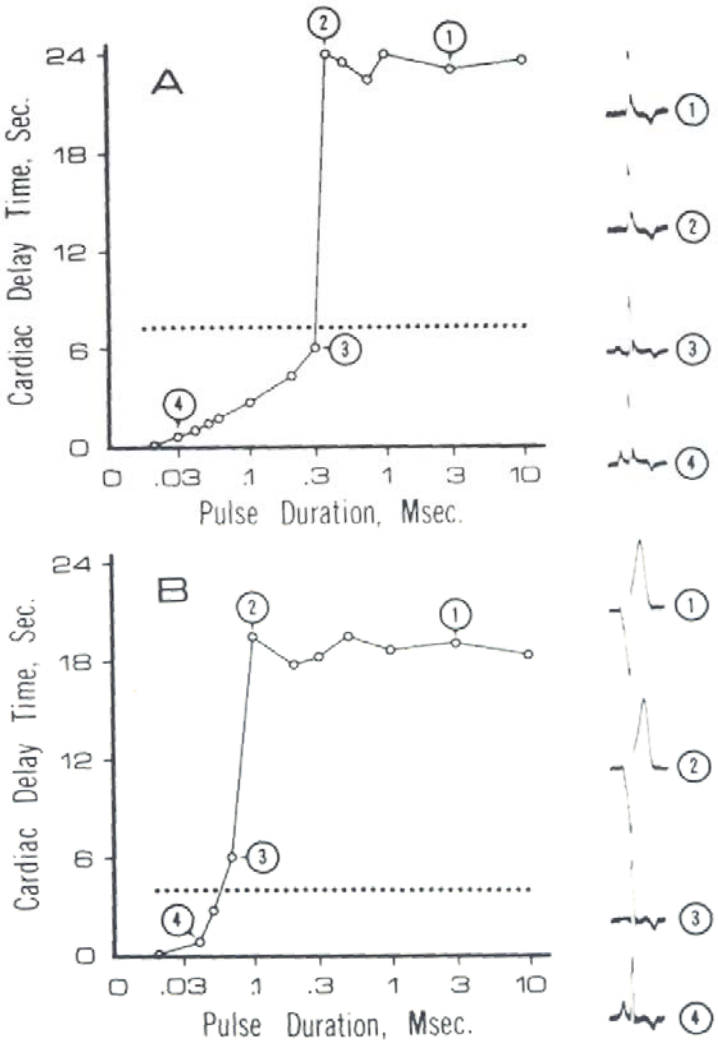
Normal automatic mechanism

A shift in the site of initiation to a region other than the sinus node can occur when **A**) the sinus rate ***slows*** below the intrinsic rate of the subsidiary pacemakers having the capability for normal automaticity or 2) when impulse generation in the subsidiary pacemakers is ***enhanced***.

A) Impulse generation by the sinus node may be ***slowed*** or inhibited altogether either by the parasympathetic nervous system or as a result of sinus node disease, leading to an 'escape' activation from a subsidiary pacemaker due to the removal of overdrive suppression by the sinus pacemaker.

B) ***Enhancement*** of subsidiary pacemaker activity may cause impulse generation to shift to ectopic sites even when the sinus node function is normal, and this may be promoted by several factors including local norepinephrine release which steepens the slope of diastolic depolarization of most pacemaker cells and diminishes the inhibitory effects of overdrive.

Normal automaticity: sinus rate reduction

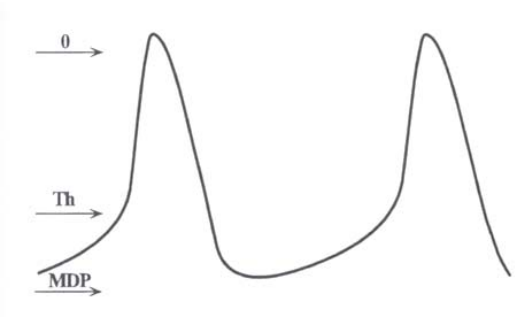


<u>Role of latent pacemaker cells in the generation of escape beats</u>: Application of increasing intensity of vagal stimulation (to elicit acetylcholine release and promote bradychardia) results in a shift of the origin of the heart beat from its normal site in the SA node to other sites in the atria or in the AV node. Further increases in stimulation intensity lead to very prolonged cardiac arrest and initiation of escape beats from the AV junction or the ventricles. Note: see the lack of p-wave in ECGs recorded during intense vagal stimulation (delay time above dotted line).

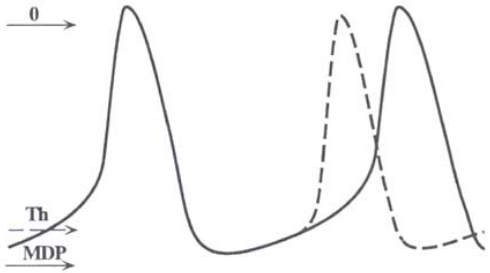
Peiss J Electrocardiol 1975

Enhanced normal automaticity

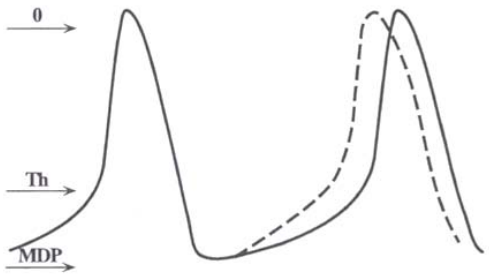
A



B

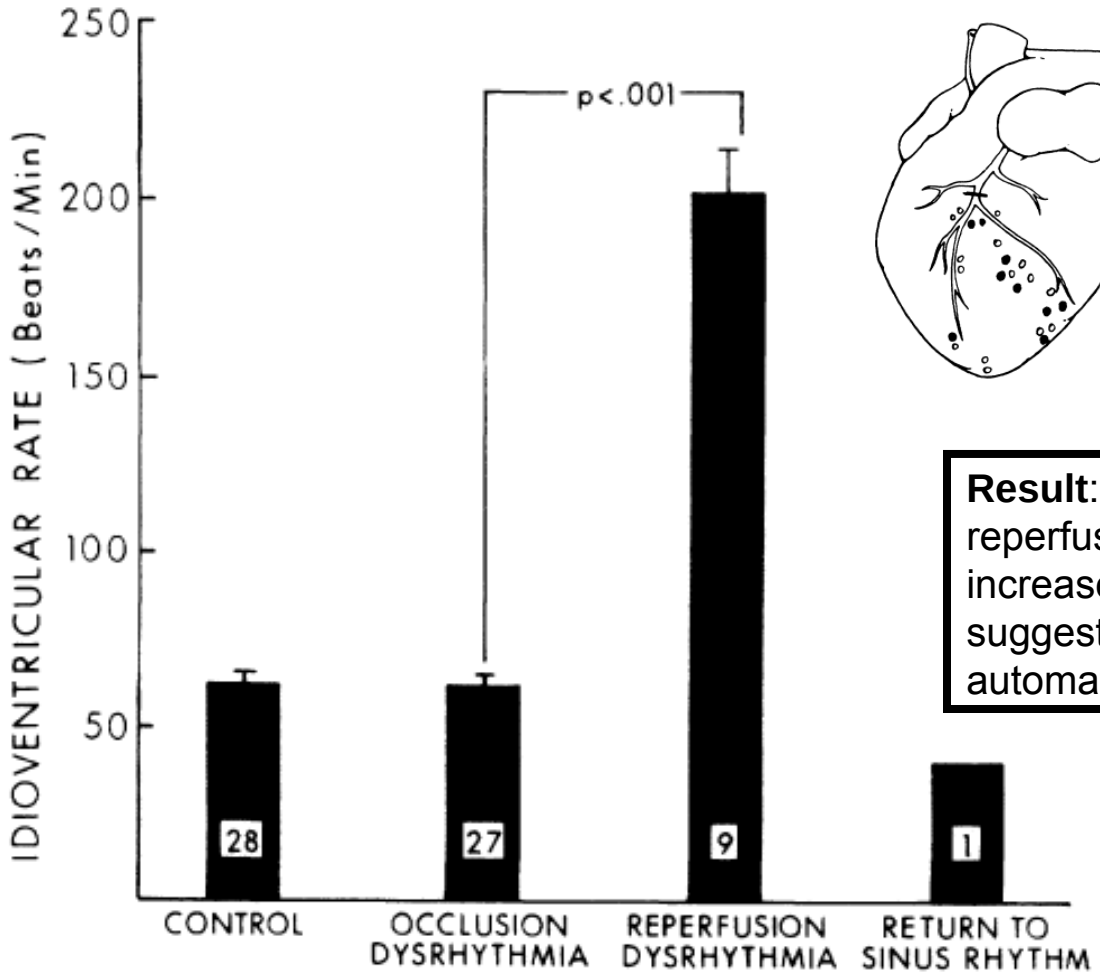


C



- Increment in threshold potential (i.e., the voltage threshold becomes more negative).
- Increase in the slope of phase 4 depolarization

Enhanced normal automaticity



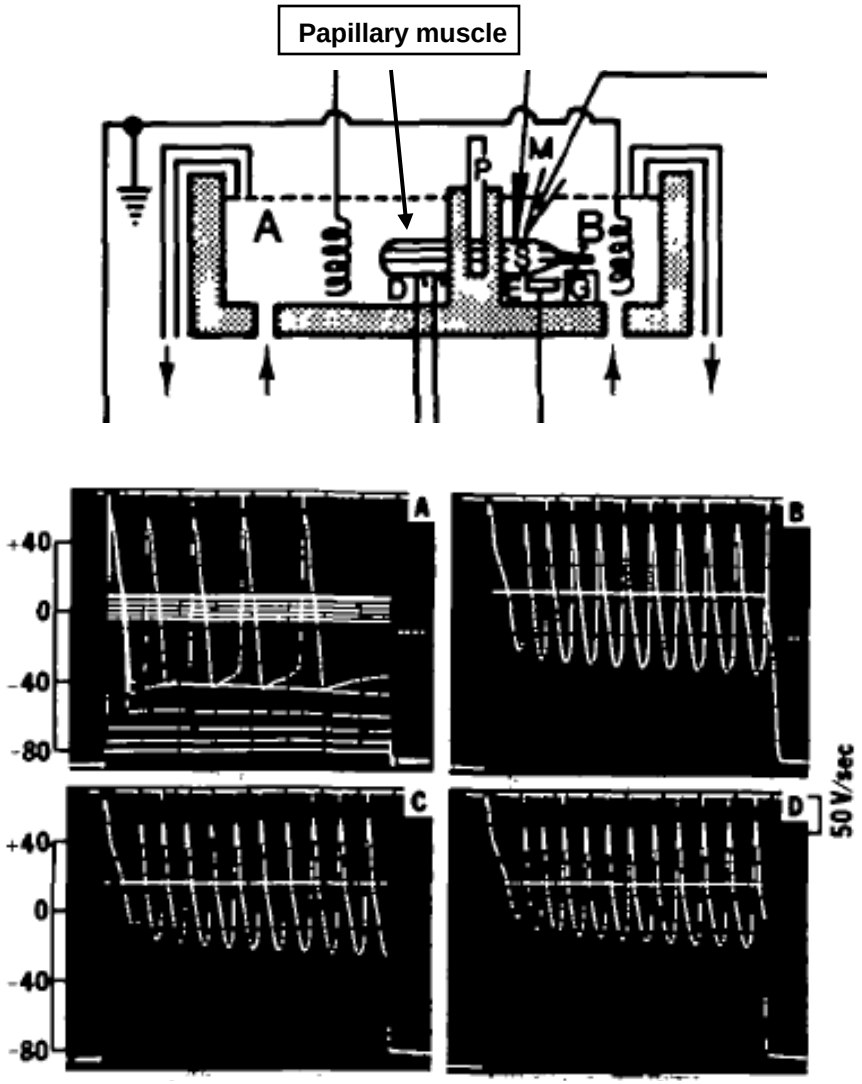
Method: In vivo occlusion and release of the left anterior descending (LAD) coronary artery to induce ischemia and reperfusion

Result: As opposed to occlusion, reperfusion consistently induced a marked increase in the idioventricular escape rate, suggesting that enhanced ventricular automaticity was occurring.

Penkoske Circulation 1970

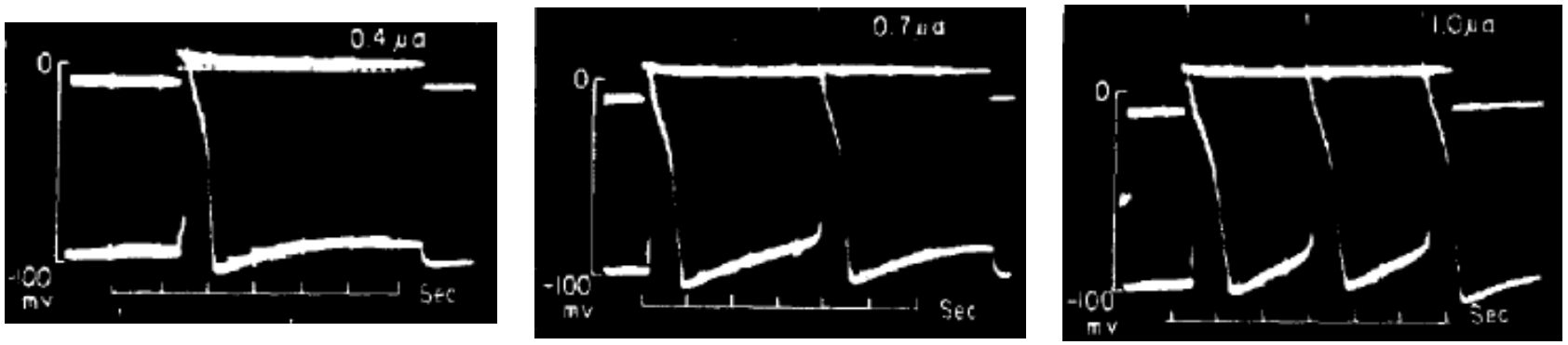
Abnormal automaticity

Working atrial and ventricular myocardial cells do not normally show spontaneous diastolic depolarization. ***Abnormal automaticity*** occurs when the resting membrane of these cell types is experimentally reduced to less than -60 mV which may elicit spontaneous diastolic depolarizations causing repetitive impulse initiation.



Imanishi and Surawicz Circ Res 1976

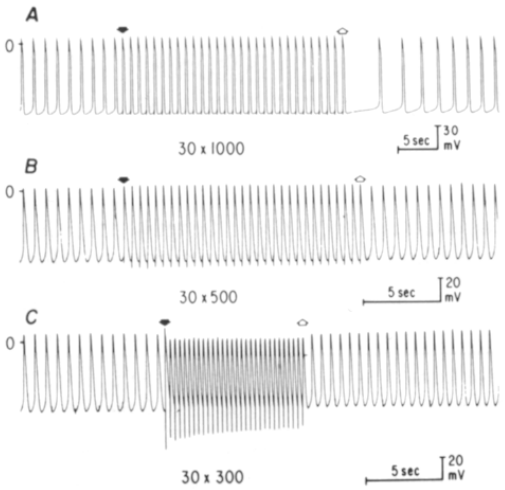
Abnormal automaticity in Purkinje fibers

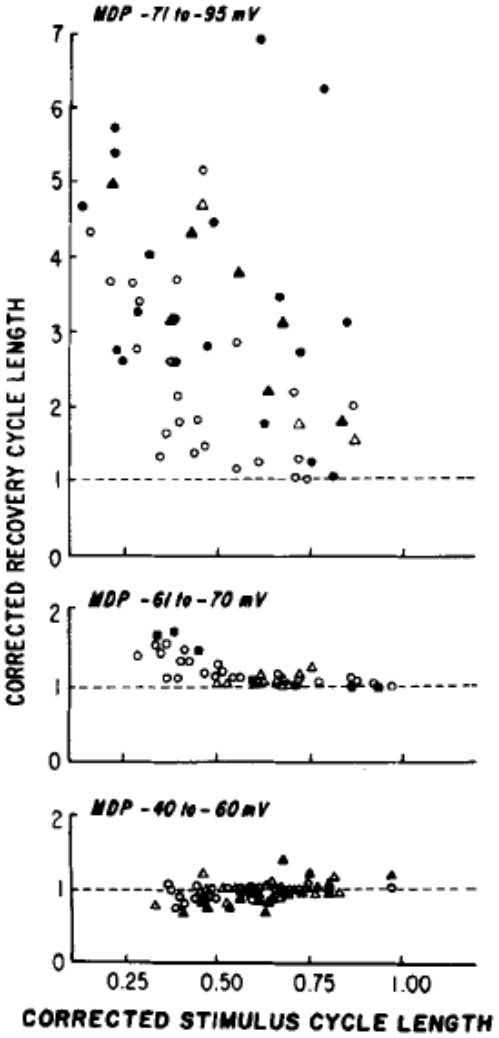


Trautwein and Kassebaum J Gen Physiol 1961

A smart way to distinguish normal from abnormal automaticity

Method: Authors perfused the preparations with different solutions in order to set the maximum diastolic potential (MDP) at three different levels.



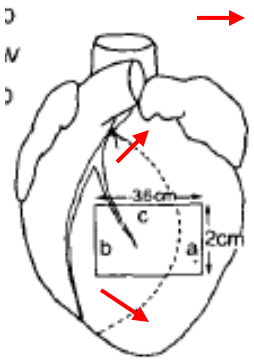


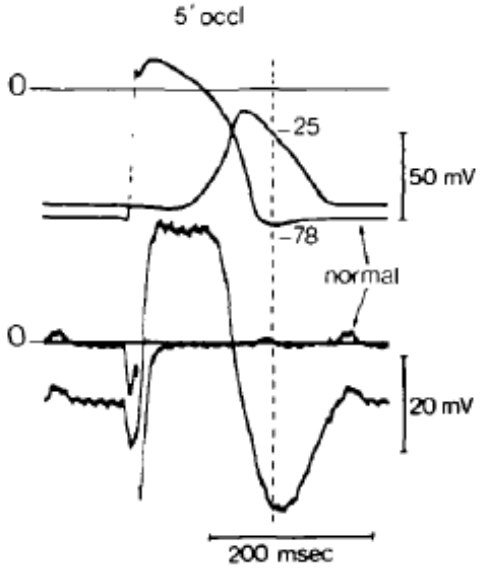
Result: Overdrive suppression of normal automaticity in Purkinje fibers bears a predictable relationship to the rate and duration of overdrive, however abnormally automatic fibers with maximum diastolic potential less than -60 mV **can NOT** be overdrive suppression regardless of the duration or rate of overdrive. Indeed, often a minor enhancement of automaticity follows the period of overdrive

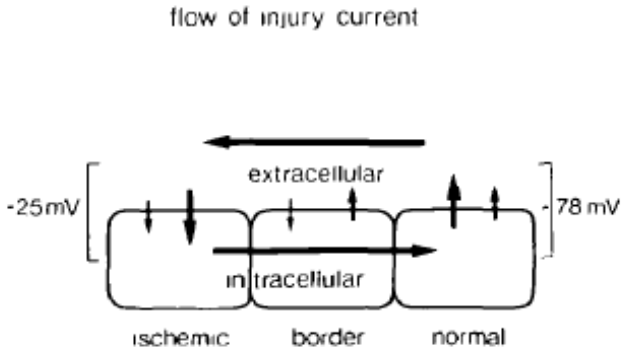
Dangman & Hoffman JACC 1983

How may abnormal automaticity be elicited in pathophysiology?

Method: Model of acute regional ischemia induced by ligation of the left anterior descending (LAD) coronary artery.





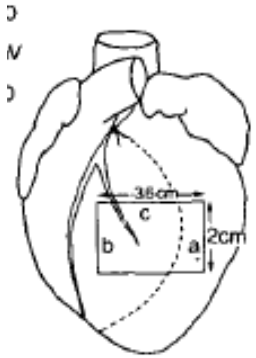


Injury currents: Local circuit currents generated between adjacent ischemic and non-ischemic cells caused by heterogeneous changes in membrane potential elicited by an infarction. The magnitude and direction of the currents change throughout the cardiac cycle and flow from ischemic cells to normal cells during diastole. Injury currents may promote abnormal automatic behavior in healthy tissue bordering the infarct.

Janse et al. Circ Res 1980

Abnormal automaticity in a model of infarction

Method: Dogs with 48 and 96 hours of infarction induced by LAD occlusion.



Result: Overdrive pacing did not lead to suppression of activity of infarcted preparations showing automaticity, which lead the authors to suggest that arrhythmias occurring in following a 48-96 hour infarction are caused primarily by a mechanism involving abnormal automaticity.

Le Marec et al. Circulation 1985

Triggered activity

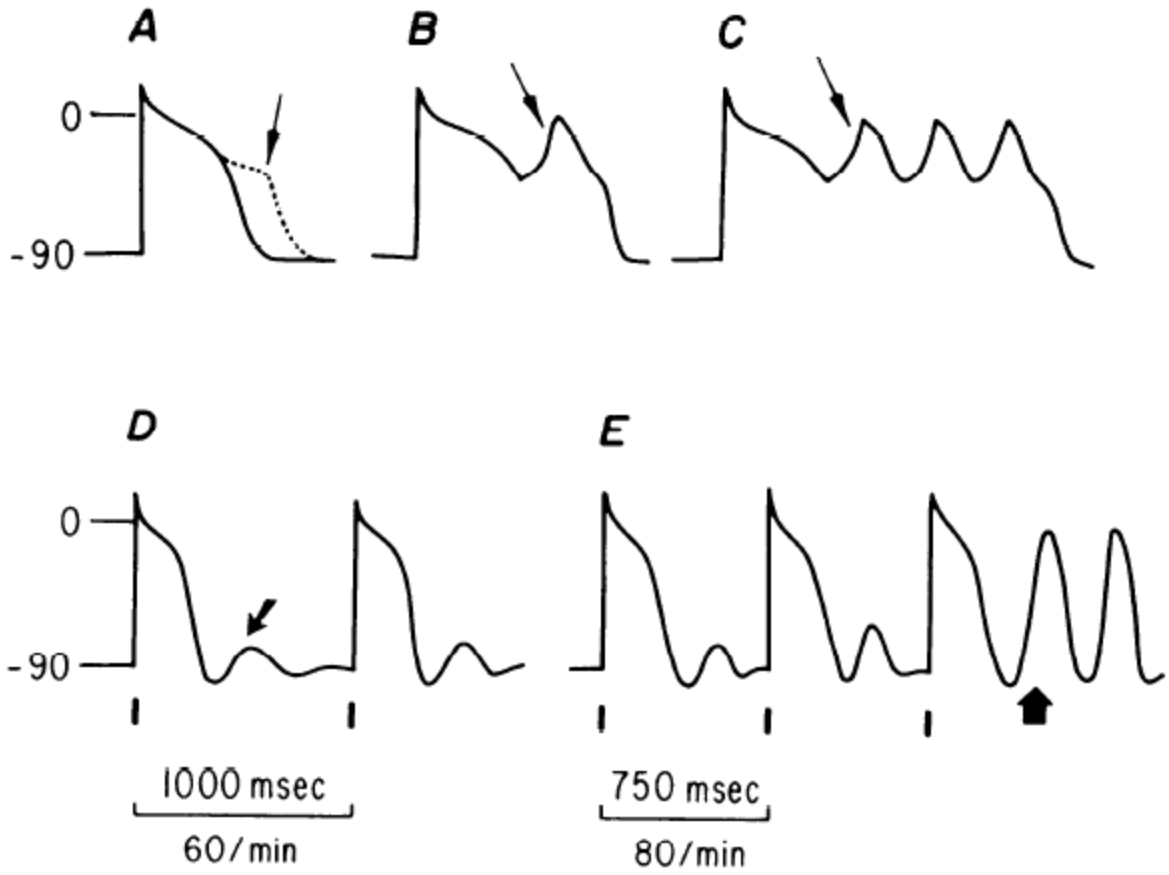
Triggered activity is impulse generation caused by ***afterdepolarizations***. An afterdepolarization is a second subthreshold depolarization that occurs either during repolarization (referred to as **early afterdepolarization- EAD**) or after repolarization is complete (referred to as **delayed afterdepolarization- DAD**).

EADs and DADs

MICHIEL J. JANSE AND ANDREW L. WIT

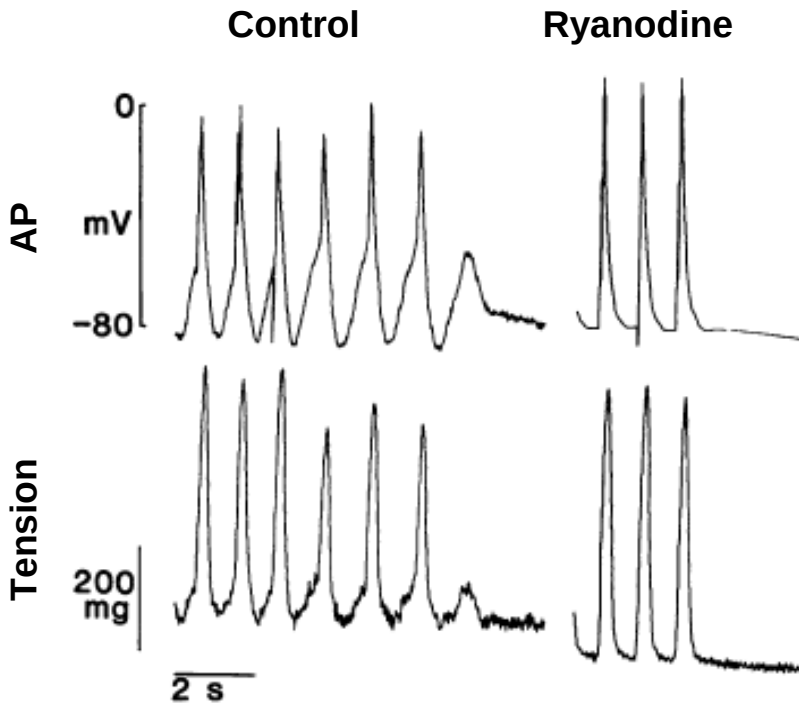
EADs

DADs



Janse and Wit Physiol Rev 1989

DADs mechanism



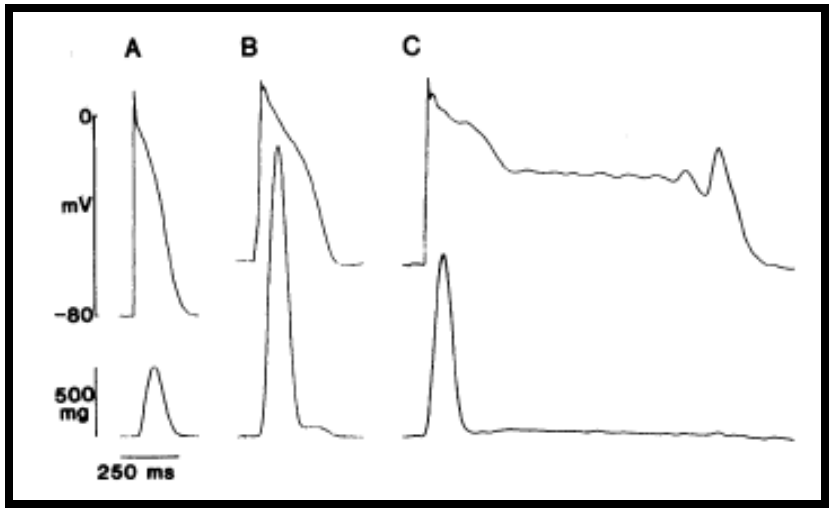
Method: Elevated Ca^{2+} plus strophanthidin and/or isoproterenol to promote DADs. Ryanodine is used to test the effect of preventing SR Ca^{2+} release on DAD incidence. BAPTA is used to chelate intracellular Ca^{2+}

Result: Both ryanodine and the Ca^{2+} chelator BAPTA prevent the formation of DADs

Conclusion: Intracellular Ca2+ overload is primarily responsible for DAD-related triggered arrhythmias

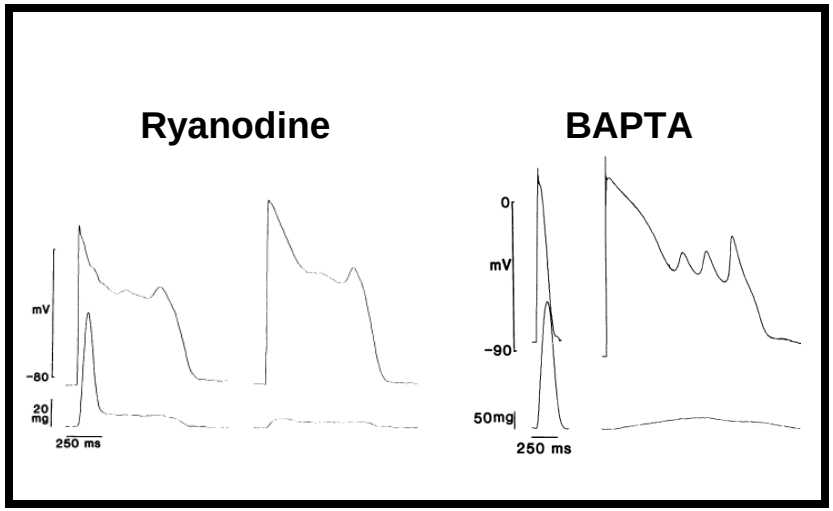
Marban et al. J Clin Invest 1986

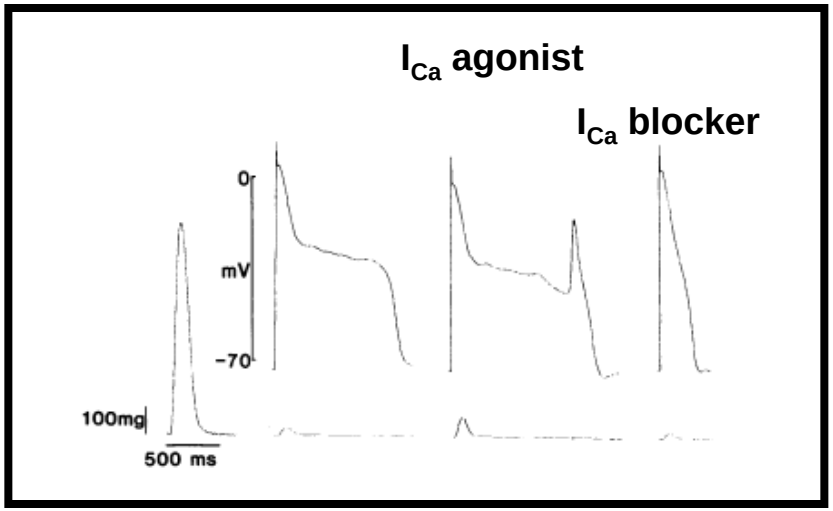
EADs mechanism



Method: Perfusion with CsCl to elicit APD prolongation and formation of EADs

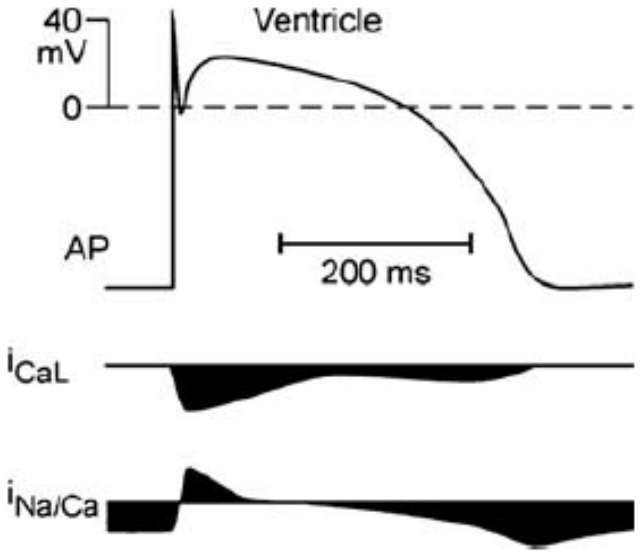
Result: Neither ryanodine nor the Ca^{2+} chelator BAPTA prevented the formation of EADs by CsCl.

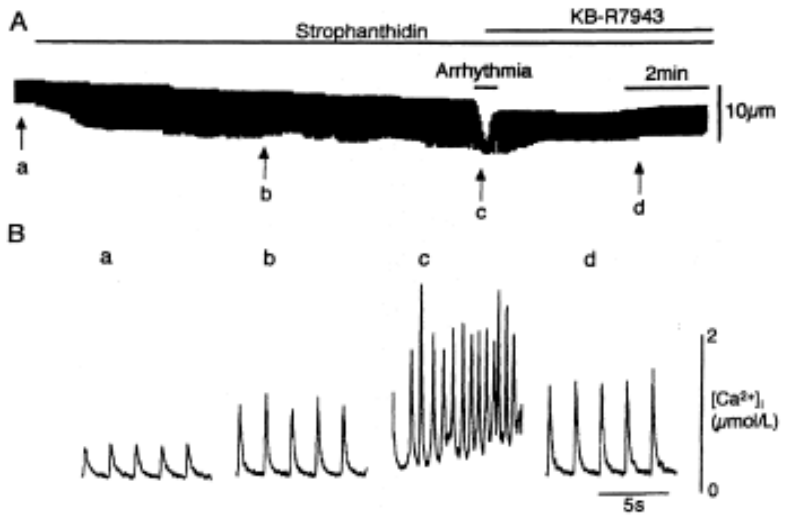




Marban et al. J Clin Invest 1986

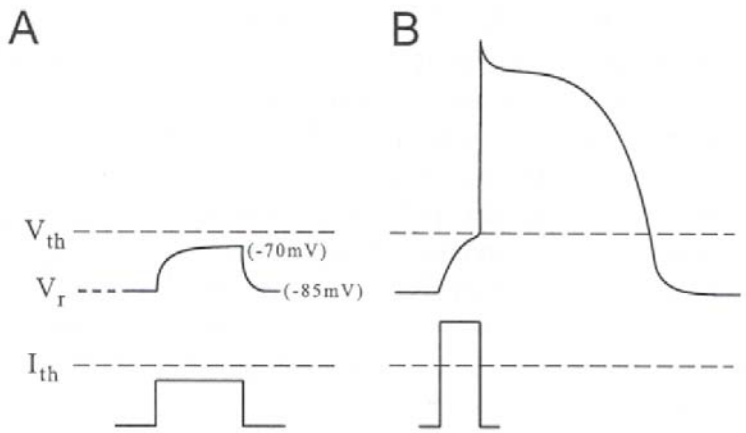
DADs induced triggered activity mechanism

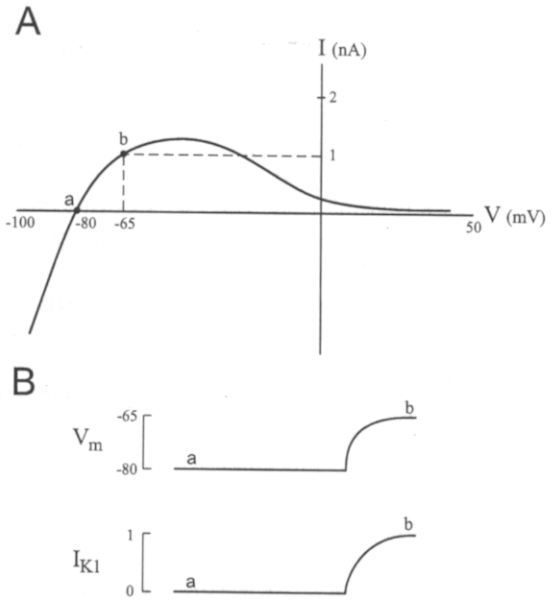




Sipido et al. Cardiovasc Res 2002

IK1


A
B
V_{th}
V_r
(-70mV)
(-85mV)
I_{th}


A
I (nA)
2
1
b
a
-100
-80
-65
50
V (mV)
B
V_m
-65
-80
a
b
I_{K1}
1
0
a
b

Bioengineering approaches

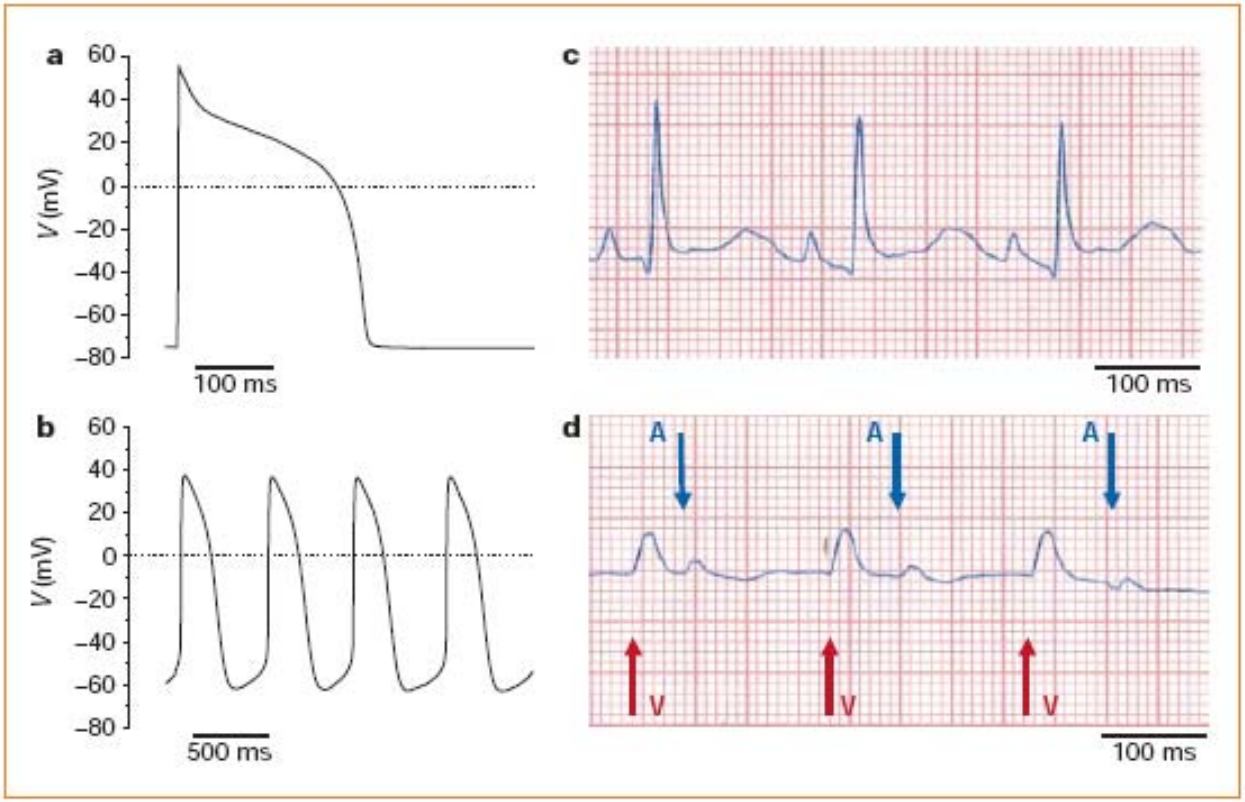


Figure 1 Suppression of Kir2.1 channels unleashes pacemaker activity. **a,** Stable action potentials evoked by depolarizing external stimuli in control ventricular myocytes. **b,** Spontaneous action potentials in Kir2.1AAA-transduced myocytes with suppressed inward-rectifier potassium current (I_{K1}; pacemaker phenotype). **c,** Baseline electrocardiograms in normal sinus rhythm (control). **d,** Ventricular rhythms for the pacemaker phenotype 72 h after transduction of Kir2.1AAA. P waves (A, arrow) and wide QRS complexes (V, arrow) 'march through' to their own rhythm.

Miake and Marban Nature 2002

Bioengineering approaches/ biological pacemakers

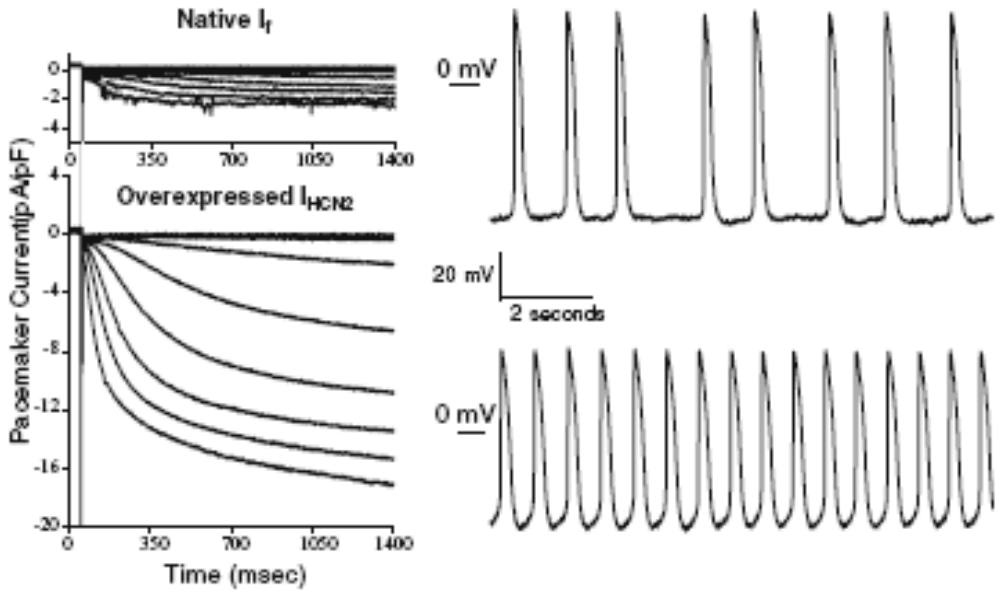
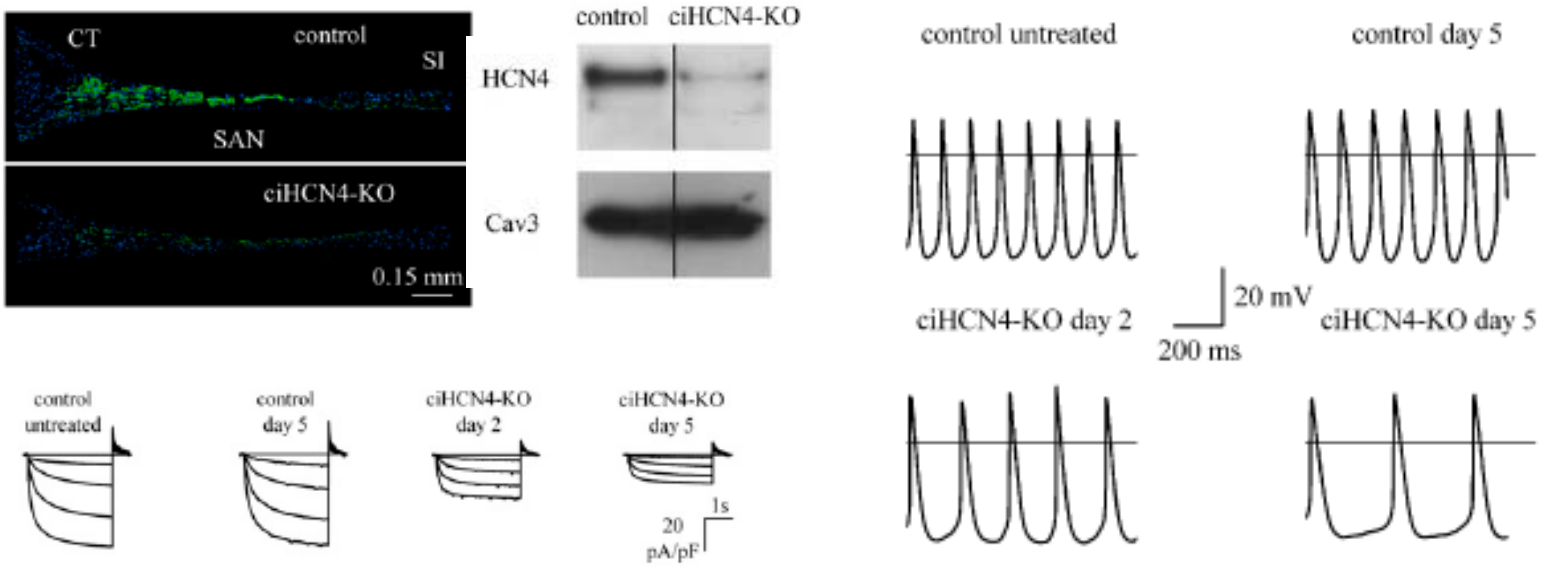


Fig. 2 Hyperpolarization activated, cyclic nucleotide gated (HCN) overexpression in neonatal rat ventricular myocyte culture increases spontaneous rate. *Left panel* Representative current traces of endogenous pacemaker current from a control myocyte expressing only green fluorescent protein (GFP) (*top*) and from a myocyte overexpressing murine HCN2 (*bottom*). *Right panel* Representative recordings of spontaneous action potentials from monolayer cultures infected with a GFP expressing adenovirus (*top*) and an HCN2 expressing adenovirus (*bottom*) (reprinted by permission from reference [9])

Rosen et al. Med Bio Eng Comput 2007

Bioengineering approaches/ biological pacemakers



Baruscotti et al. PNAS 2011

Group work

Why do we care at all to understand the mechanisms of arrhythmia?

END

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