Control of Chaos in the Heart.

Shock energy decreased >10 times

What is next?

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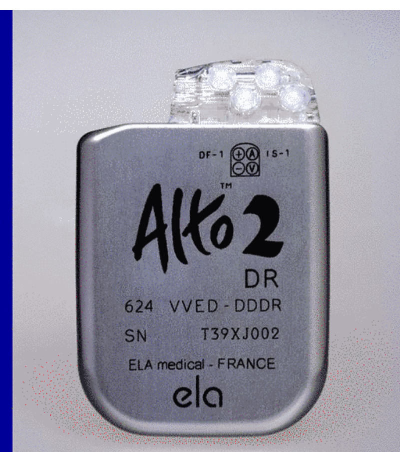
Implantable Defibrillator (ICD)

can terminate chaos in the heart by using successively:

1. Anti Tacycardia Pacing (ATP);
2. If it fails, then Cardioversion;
3. If it fails, then the defibrillator discharge.



Ela Medicale ICD, Paris

Comments:

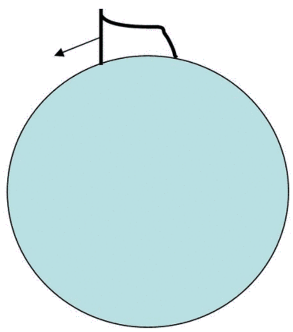
1.ATP is a less damaging intervention

2. Cardioversion pulse ~5J, synchronized with ECG.
Not used anymore (has no advantages over ATP).

3. Defibrillator: a large energy shock ~30J

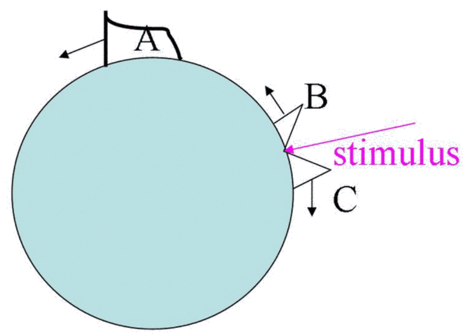
Textbooks: mechanism of ATP (1dim)

.A stimulus delivered to rotating pulse itself, will produce no effect since the tissue is refractory



Reentry

A stimulus delivered far from the rotating pulse, will produce 2 counter -propagating pulses.

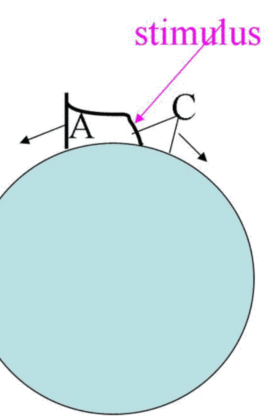


A and C will annihilate.
B will continue rotating.

Text books:

A stimulus delivered to tail of AP can create ONE pulse (C)

Time interval when it is possible, is called Vulnerable Window (VW).



A and C will annihilate.
Tachycardia will be terminated

No understanding of ATP in 2 d or 3d is in the cardio Textbooks.

Defibrillation today

only technical questions were considered important :

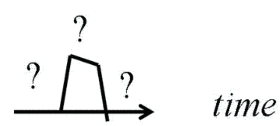
Should the shape of the defibrillation pulse be: exponential, or truncated exponential?or a half of a sinusoid? Or 2 pulses together (bi-phasic pulse) will be better?

Such bi-phasic pulse

gave 30% decrease of defibrillation energy.

Mechanisms why it is better were understood (Ideker, Fast, I.Efimov).

Medtronic and other companies regularly supply experimental labs with grants ($100,000) to investigate effects of increasing front slope, decreasing time contants etc on defibrillation.



Control of rotating waves - a new target for defibrillation

We formulated the problem differently : why a defibrillatinting shock has such a huge amplitude, in spite of all parameters adjustments ?

4,000 V, 15 A , 5 ms, 300j,
or in implanted devices, same Electric Field (~5.6 V/cm), ~ 30 J ?

Because it is aimed at destruction of ALL waves in the heart, while dangerous are only rotating waves.

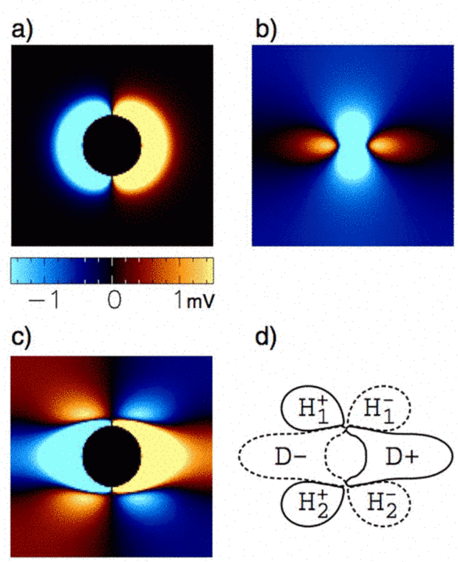
So, the target of defibrillation may be changed.
It should be control of rotating waves, and not termination of all waves.
This may work in specific cases only, but give substantial advantages.

Control of Spiral Waves

1.Drift of a spiral in a parameter gradient is understood, but we have no tools to control these gradients in the heart.
2.Drift of a spiral wave can be induced by pacing with period T<T_spiral, Agladze 1984 (experiment on BZ), Pertsov.
3. Resonance drift induced by flashes of light on BZ, Agladze, Mikhailov 1985.
This topic intensively continues even now, interesting math tasks (Biktashev, Zykov, Hakim, Karma).

The theory now reached the level where we may try to control rotating waves in the Heart, not in theory or in model experiments only

Near every obstacle, a far field pulse creates depolarization and hyperpolarization



These are called virtual electrodes (Wikswo et al).

Same pattern is created near an obstacle around which an anatomical reentry rotates.

We proposed to use this effect to provide a direct access to the reentry core. Thus terminate a reentry in the same way as if an ATP simulating electrode would be put exactly to the reentry core.

Pumir, Krinsky, JTB, 1999

The depolarization required is same small as needed for ATP.

Same as with ATP, a pulse can terminate reentry only if applied at a well specified phase of reentry rotation (Vulnerable Window, VW)

Advantages vs ATP;

the virutal electode is situated on the reenrry core, and not far from it as with ATP.

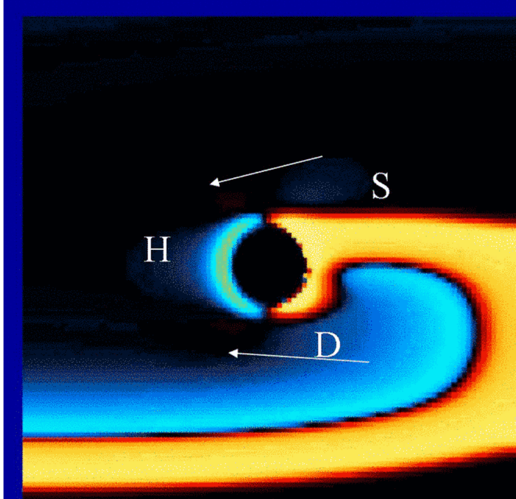
Pumir, Plaza, Krinsky. Control of rotating waves in cardiac muscle: analysis of the effect of the electric field. Proc Roy Soc B, 257, 129-134, 1994.

Huyet et al, Unpinning of a vortex..., Int. J.Bifurc. Chaos, 8, 1315, 1998.

Pumir, Krinsky, Unpinning of a rotating wave…, J.Theor.Biol, 199, 311,1999.

Krinsky, chapter 37 in "Cardiac Electrophysiology", Zipes &Jalife, eds , 1999.

Virtual electrodes (H, D) position when an electric field is applied during Vulnerable Window (VW)

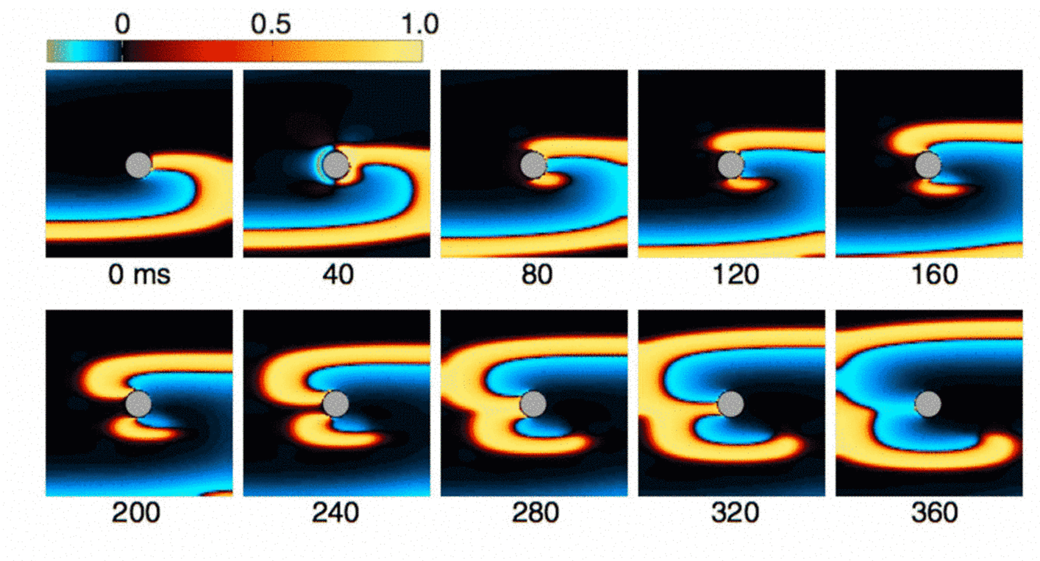


S- a spiral wave,
H and D- Hyperpolarized and Depolarized regions created by an electric field.

Waves S and D will collide and annihilated (see arrows).

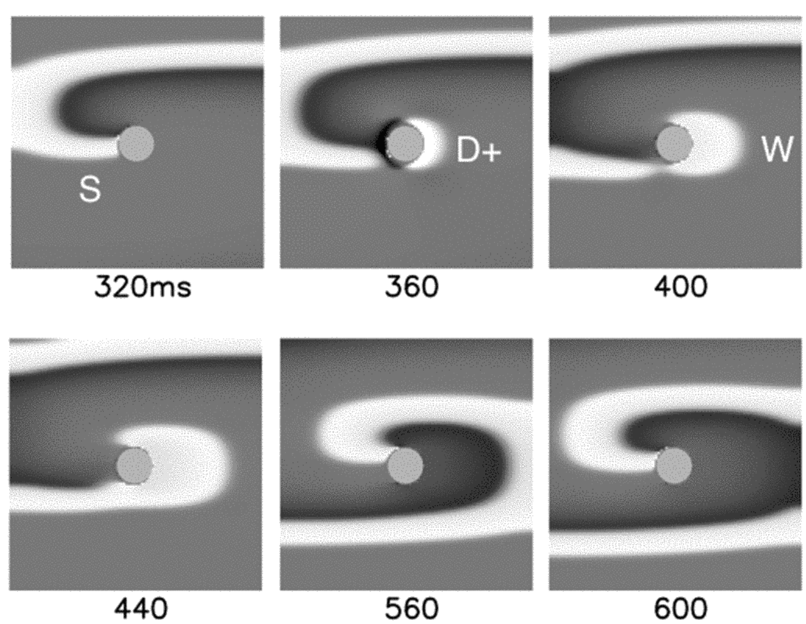
With another timing of the electric field pulse, this will not happen.

Termination of a reentry: shock 0.52 V/cm properly timed



No termination: shock 0.52 V/cm not properly timed

Wave from D+ propagates in both directions.



Comparing with ATP

The results above are easy to understand:

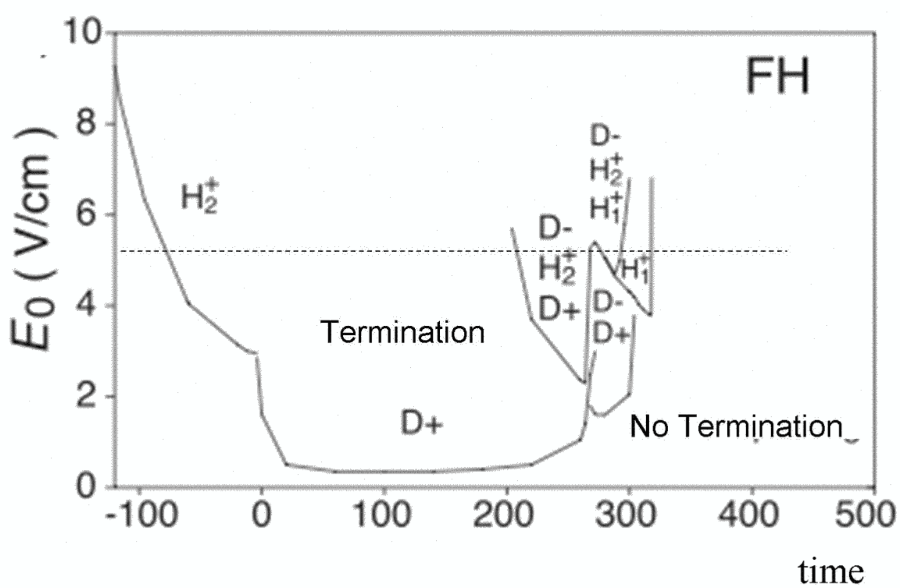
Termination Window (TW) by an electric field pulse has same mechanism as the vulnerable window (VW) for ATP (one stimulus S2 in S1-S2 protocol).

With an important difference:
-for S1-S2 protocol : position of the reentry should be known,
and the stimulating electrode should be placed on the reentry path or close to it.

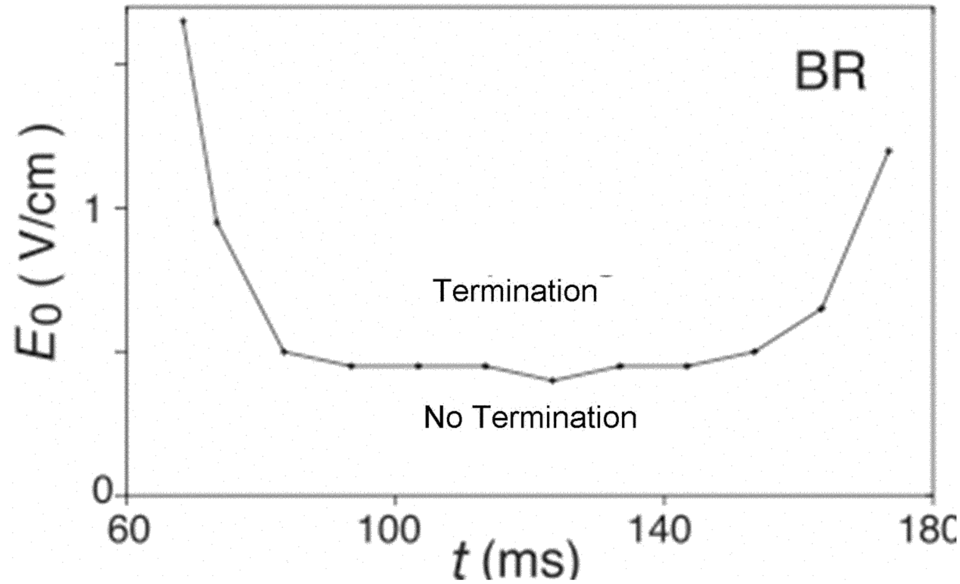
-for an electric field pulse , no matter where a reentry is situated.

Dependense on the rotation phase

Compare with: 5.4 V/cm - defibrillating electric field



Termination time window (low-voltage part)



5.4 V/cm - standard defibrillating electric field

Energy can be decreased 100 times

Thus, theory and numerical simulations showed that a reentry can be terminated by an electric field ~0.5 V/cm. Since the defibrillating electric field is ~ 5.6 V/cm (E_80), this means that the Electric field E can be decreased an order of magnitude, thus the energy- decreased by two orders of magnitude (since energy ~ E^2).

This result was obtained for sufficiently large obstacles, R> 3λ.

Bidomain equations

The bidomain model describes the extracellular potential, ϕ_e, and the intracellular potential, ϕ_i

$$\nabla \cdot \sigma_i \nabla \phi_i = \beta \left[C_m \frac{\partial}{\partial t}(\phi_i - \phi_e) + I_{\text{ion}} \right] - I_i, \quad (1)$$

$$\nabla \cdot \sigma_e \nabla \phi_e = -\beta \left[C_m \frac{\partial}{\partial t}(\phi_i - \phi_e) + I_{\text{ion}} \right] - I_e, \quad (2)$$

where σ_i and σ_e are the conductivity tensors, I_i and I_e are the currents coming from external sources, injected in the intracellular and extracellular spaces, respectively. β and C_m are parameters; I_{ion} is the ionic current.

An obstacle in the Bidomain model

An obstacle has been modelled by assuming a zero current across the tissue's boundary:

$$\nabla(E + \mathbf{E}_0 \cdot \mathbf{x}) = 0$$

Here E_0 is an external electric field

Bidomain effects

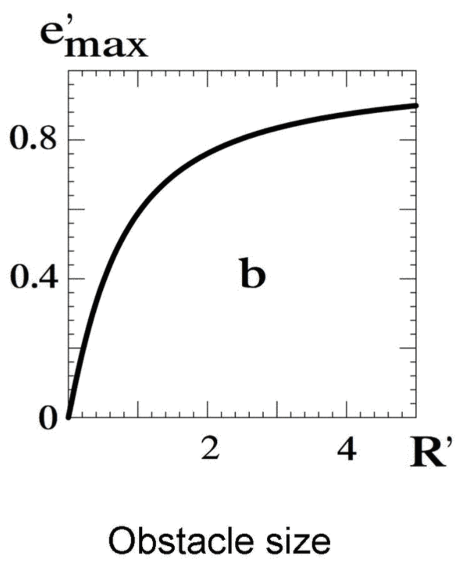
For large obstacles, the amplitude of membrane potential change e_{max} is about

$$e_{max} \approx \lambda E_0$$

This can be easily understood by analogy with the purely one-dimensional problem, where e decays exponentially with the space constant λ. For smaller obstacles, e_{max} is diminished, and e_{max} -->0 when the obstacle size d-->0 in 2-dimensional media. A simple analytic solution may be found in the case of a circular obstacle. Linearizing the equation of motion near the resting state, one obtains

$$\nabla^2 e - e/\lambda^2 = 0$$

Depolarization amplitude is larger for large obstacles



Dimensionless values for obstacle size R' and depolarization e' are given.

R'= R / λ, where R is Radius of the anatomical obstacle, λ is an electrotonic constant, ~ 0.5-1mm

e'= e/e_max, where e is depolarization induced by an electric field, and e_max is its value for a very big obstacle.

Pumir, Krinsky JTB 1999.

Comparing with the heart

As seen from the graph, if the obstacle around which an anatomical reentry rotates is $< 3\ \lambda$, the gain in energy decreases.

Around what size obstacles the reentries rotate in the heart?
Theory can't give answer this question.
But upon the answer, depends how large will be the gain in energy in the heart, or even if any.

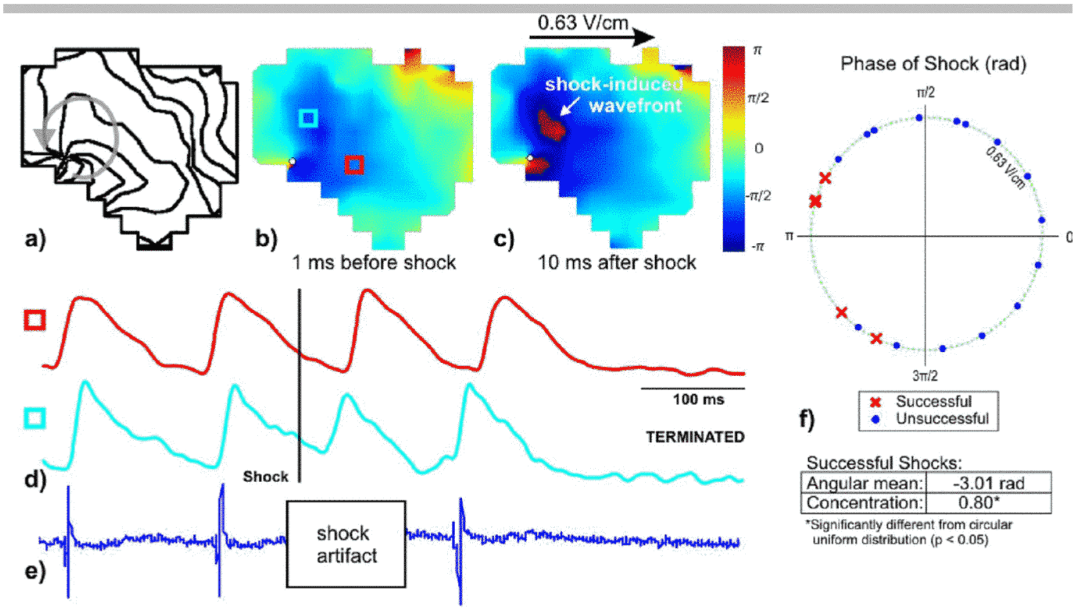
Here, an experiment is needed.

A path to experiment…

We published these results in 1999 (JTB). They went unnoticed, no reaction at all.
In 2003, we contacted experimenters. Naturally, they did not believe our theoretical (computer assisted) estimates and requested to repeat the calculations on the full bidomain model. We did it, and published results in PRL, 2004. Unexpectedly, there was Focus of American Physical Society devoted to this our article, and then Nature News.

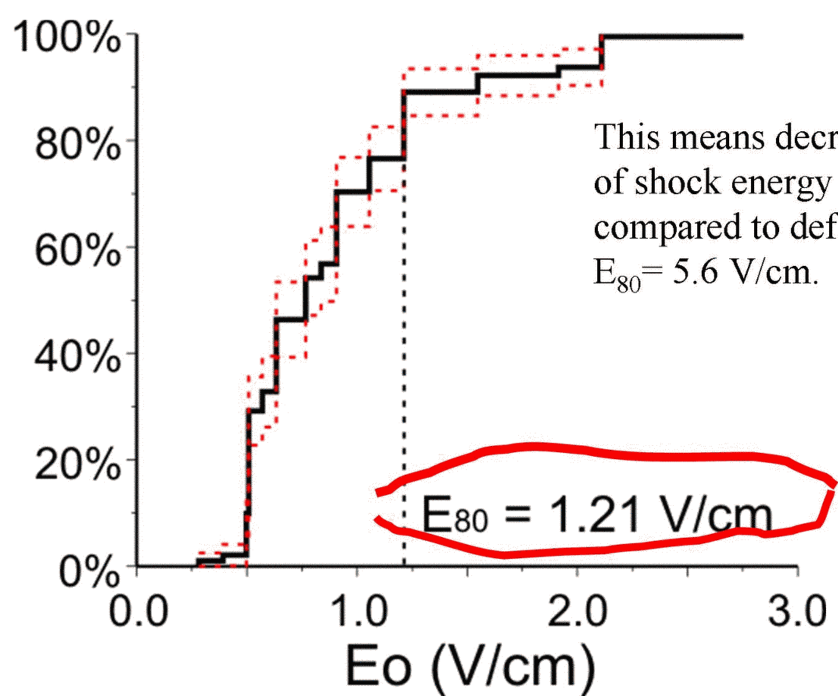
Such an appreciation appeared enough to justify expensive experiments.

Termination of reentry by a shock. Rabbit RV (Nikolski, Ripplinger, Efimov)



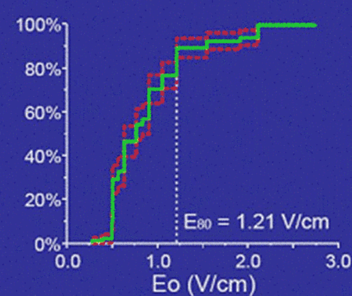
10 ms isochrones. (b, c) Phase-plane maps. (b) 1 ms before shock..(c) 10 ms after shock a (d) Optical traces show two more rotations after the shoskl (e) Local ECG recording (f) Polar plot of successful and unsuccessful shocks.

Terminated reentries versus shock strength (exper, lab Efimov)



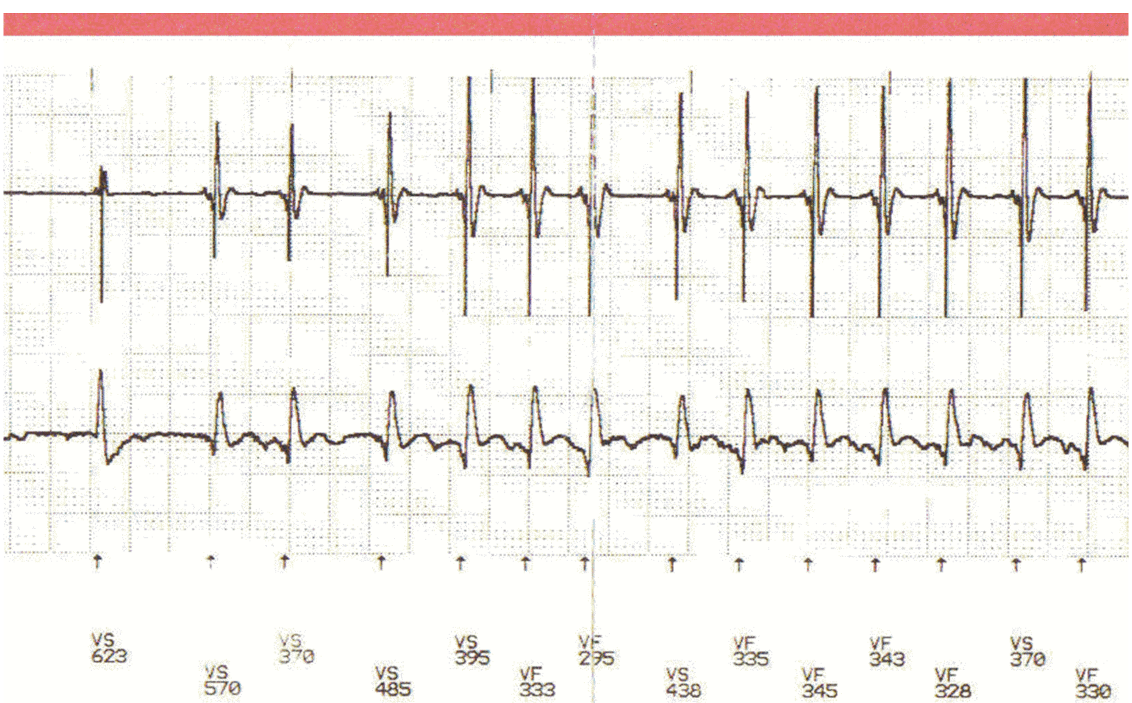
This means decrease of shock energy 20 times compared to defibrillating E_{80}= 5.6 V/cm.

Survival analysis of terminated reentries versus shock strength



Green line indicates observed terminations, red dashed lines correspond to 95% confidence intervals. E80 (shock strength at which 80% of reentries were terminated) was 1.21 V/cm, which corresponds to 6.6 times the average field excitation threshold.
All reentries were terminated at shock strengths at or below 2.74 V/cm.

Ripplinger, Krinsky, Nikolski, Efimov.
Mechanisms of unpinning and termination of ventricular tachycardia
Am J Physiol. 2006 ;291(1):H184-92.



When ICD detected fibrillation, EGM is not chaotic yet

Courtesy Dr. L.Tereshchenko

Limitations:

- an early stage of a reentrant arrhythmia

-a reentry rotating around a large obstacle (radius $>3\lambda$, λ=0.5mm)

-may induce VF*

- after unpinning, may repin to another obstacle*

*- *tools to ovecome these limitations are developed; not tested in experiments yet.*

Advantages:

-Shock energy was decreased 20 times in experiment, (theoretical limit ~ 100 times). The larger the obstacle the more gain.

- Can be used effectively in automatic implanted devices that can detect an arrhythmia early.

Conclusions to part 1: UnPinning

1. Far Electric Field provides a direct and not invasive access to an anatomical reentry circuit.
2. A weak shock from defibrillating electrodes creates membrane polarization around every anatomical obstacle. This polarization can serve to extinguish the arrhythmia if delivered in right time .
3. In experiment, 20 times decrease of shock energy was demonstarted in healthy rabbit right ventricles, and in infarcted hearts.
4. The method was developed to work with a specific mechanism of arrhythmia : an anatomical reentry rotating around a relatively large obstacle, radius $> 3\lambda$, where λ is the electrotonic constant (~0.5mm). It is expected to work in implanted devices able to catch initial phases of VF and AF.

ATP- Anti Tachycardia Pacing

Anti Tachycardia Pacing (ATP)

succes rate of ATP is not 100%
There are no clear physical mechanisms explaining it (L.Glass)

--> a challenge for both, physicists and MD

-increase success rate of ATP will eliminate many of damaging and painful defibrillating shocks

Sucess rate of ATP

decreases with distance to the core

A train of stimuli applied away from the core (7- to 8-mm distance) terminated 5 of 24 episodes of reentry (success rate 20%)

\

When it was applied near the core (within 1.6 mm)
It terminated 14 of 17 episodes of reentry
(success rate 80%, P<.001).

sustained episodes of functional reentry with a stationary core,
isolated swine ventricular slices.

Kamjoo K, et al, Circulation. 1997

Physics is needed to go beyond 1 dim

Mechanisms of ATP described in the textbooks are valid for 1 dim only
No understanding of ATP in 2 dim or 3dim is in the cardio Textbooks.

But here may be the key for understanding why % success ATP is not 100%, and what can be done to increase it.

Disagreement: theory - card experiment

Theory showed that a wave train can terminate a free spiral wave with 100% success, no matter how far from the core the stimulating electrode is situated.

Cardiac experiments show success rate < 100%.
So, rotating waves were not free in these experiments (= pinned to obstacles).

Pinning Force

Which defects act as pinning centers?
We proposed a way to study this general problem by using an advection field to quantify the attraction between an obstacle and a vortex.

. When the drift velocity is large enough,the pinned vortex is detached fromt he obstacle , whereas, in the case of a small drift velocity, the vortex remains attached to the heterogeneity.
The limiting velocity provides an estimate of the pinning force.

Pazo,Kramer, …,Krinsky,
Pinning force in active media,
PRL. 2004 93(16):168303

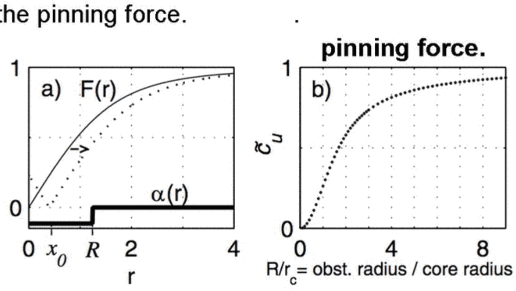


FIG. 1. Pinning and depinning in the GL model. (a) A small drift term (arrow) shifts the vortex (dotted line); see Eq. (1). (b) Normalized unpinning velocity $\tilde{c}_u = c_u/c_u^\infty$.

$$\partial_t A = [1 + \alpha(\vec{r})]A - |A|^2 A + \Delta A - c\partial_x A. \quad (1)$$

advection

Barkley model

$$\partial_t u = f(u, v, r) + \nabla^2 u - c\partial_x u,$$
$$\partial_t v = g(u, v) - c\partial_x v.$$

$$f(u, v, r) = \epsilon^{-1} u(1-u)\{u - [v + b(r)]/a\},$$
$$g(u, v) = u - v.$$

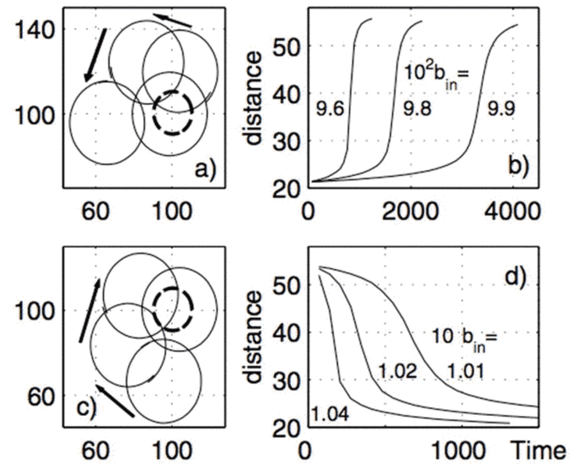


FIG. 2. An obstacle with $b_{in} < b_{out}$ does not pin a spiral wave (a),(b), whereas with $b_{in} > b_{out}$ pins it (c),(d). (a) A rotating wave is expelled from an obstacle (thick dashed line) with $b_{in} = 0.099$ and $b_{out} = 0.1$(corresponding to $r_{c,in} = 2.18$ and $r_{c,out} = 2.32$). The trajectory of the tip for four rotations at different times is shown. (b) Maximal distance per period to the center of the obstacle as a function of time for three values of b_{in}. (c) Same as (a) with $b_{in} = 0.101$ (corresponding to

Pining Force

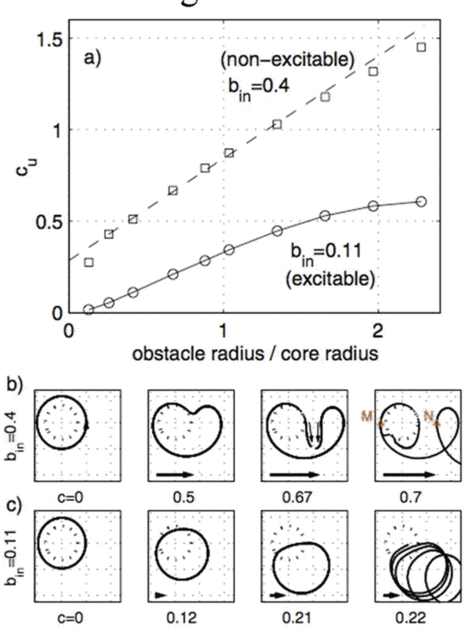
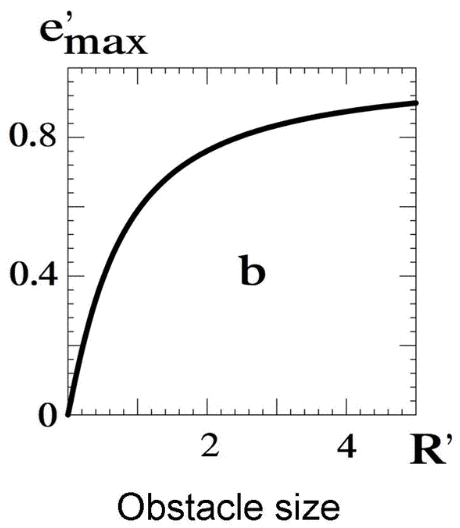


FIG. 3 (color online). Unpinning by an advective field. (a) Unpinning velocity as a function of the obstacle radius ($b_{out} = 0.1$). The dashed line is a straight line with slope $2r_c/T$. (b),(c) The routes from a pinned rotating wave to a free one. ($R/r_{c,out} = 0.67$). $r_c(b = 0.1) = 2.32$ and $r_c(b = 0.11) = 6.13$.

Pinning Force increases with size of the obstacle.

ATP (a wave train from a remote electrode) can do nothing with large obstacles -Pinning Force is too big.

Unpining vs ATP



ATP can do nothing with big obstacles (Pinning Force is big).

Unpining can do nothing with small obstacles (depolarization induced by a far field is too small)

Far Field Pacing (FFP)

can be proposed as a tool to increase ATP success rate

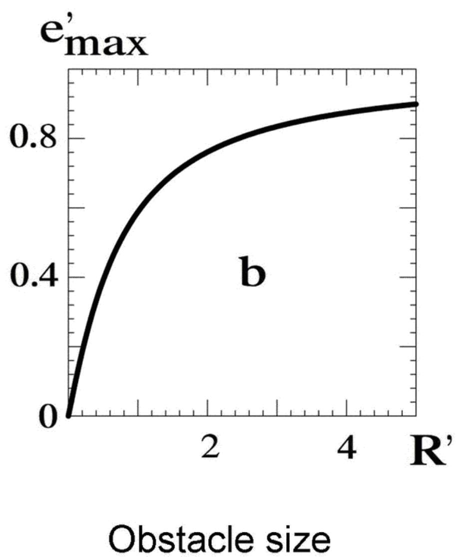
Far field has access everywhere, and can be used for pacing from virtual electodes

It is equivalent to pacing from multiple locations but only one electrode is connected to the heart and to the device.

- It may be useful when mechanisms of ATP failure are pinning or a big distance of the pacing electrode from the core.
  It is estimated to give additional 5-10 times gain in energy compared to unpinning

.

Depolarization amplitude is larger for large obstacles



So, the depolarization reaches the stimulation threshold only near big size obstacles.

Increasing the energy, one may increase the number of (virtual) pacing electrodes

It is this feature that gives higher success rate to FFP.

QuickTime™ et un décompresseur H.264 sont requis pour visionner cette image.

1 pacing electrode

N.Otani

2 pacing electrodes

N.Otani

QuickTime™ et un
décompresseur H.264
sont requis pour visionner cette image.

3 pacing electrodes

N.Otani

QuickTime™ et un
décompresseur H.264
sont requis pour visionner cette image.

Examples

1. Success rate of ATP decreases with distance from a pacing electrode to the reentry path. FFP will have no problems here

2. Allessie tried entraiment of AF.
He found that areas about 4 cm can be entrained,
but not the whole atria.

Pacing from several electrodes distributed over the atria,
was not yet technicallly realistic at that time.
FFP makes it possible

FF pacing may be painless

UnPinning, Rabbit experiment, gave E_80= 1.2 V/cm (Efimov lab),
Compared to 5.6 V/cm, the Shock Energy decreased 20 times
(Energy ~ voltage squared).

FF Pacing, terminates AF and initial stage of VF with 0.4 -1 V/cm,
in canine hearts. Its min corresponds to (0.4/5.6)^2= 0.005 =
1/200 DE (defibrillating energy). It is
- ~10 times less energy than UnPinning
- below the pain threshold

Theory:Pumir, Krinsky: Proc RoySoc 1994, JTB 1999,
PRL 2004, Focus of Amer Phys Society, Nature News.

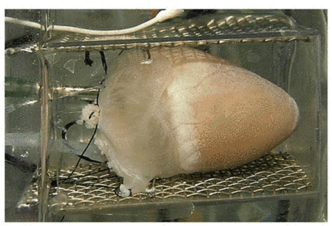
Far Field Pacing (FFP)

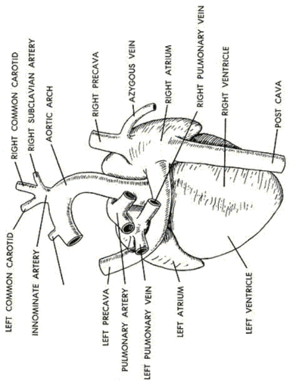
- For pulses <1/400 of defibrillation energy (DE)
FFP is just the conventional ATP
that uses the defibrillating electrode for pacing.

-For pulses~1/200 - 1/50 DE, FFP is an extended version of ATP,
where the pacing stimuli arise from multiple locations in the atrial muscle, secondary to virtual polarizations at numerous local heterogeneities.

Rabbit experiments

Far Field Pacing effects on AT and AF were preliminary tested in Rabbits whole hearts (LangendorfPerfused)
by V.Nikolski , September 2005.





Experiental set up 1s

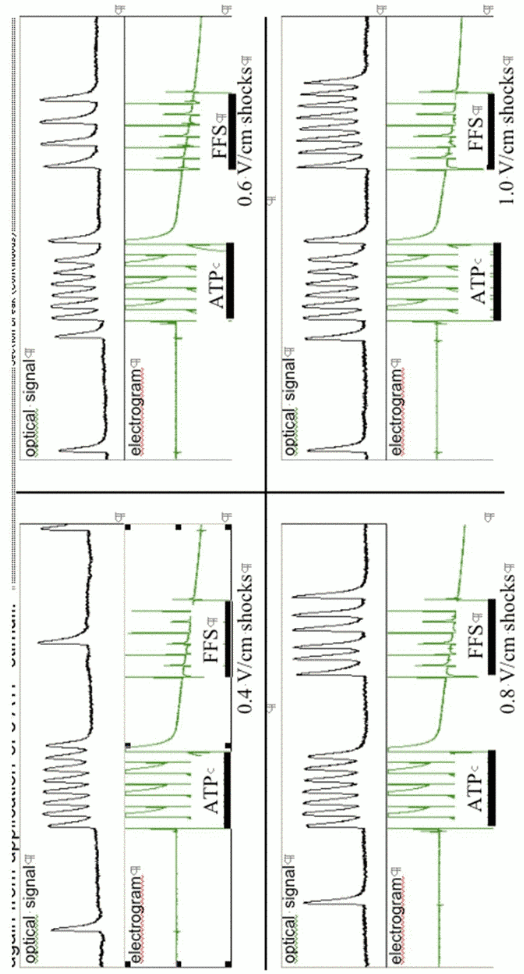
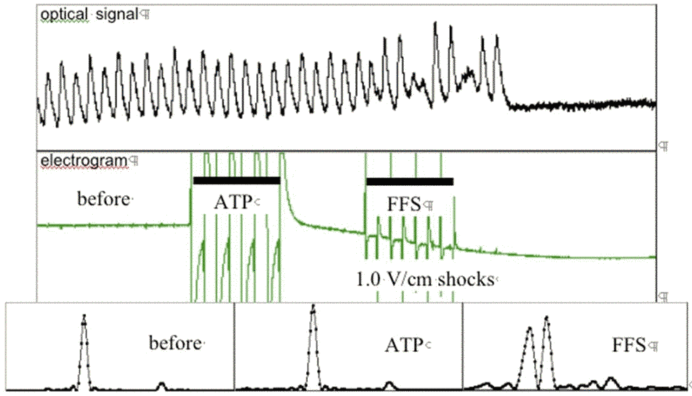


Figure 2. Threshold determination for far-field stimulation (FFS). The optical signals and surface electrogramms during application of 4 different FFS strengths are shown. Upper traces: 3.5 sec optical recording showing optical atrial action potentials recorded during last SA node derived beat, ATP induced beats, and far-field stimulation shocks induced beats. Lower traces: bipolar electrogram, recorded at the location of ATP electrode. The timing of ATP and shock application is visible via large stimulation artifacts. Duration of ATP and FFS was 630ms (black bars).



Iin this preparation,
1V/cm
is the excitation
threshold

Figure 4. Termination of AT after far-field stimulation (FFS). In this case the FFS entrained the
AT causing its self-termination after 2-3 rotations. Black upper trace traces: optical recording showing optical atrial action potentials recorded during AT, ATP, FFS, and during post-stimulation termination. Green trace: bipolar electrogram, recorded at the location of ATP electrode. The timing of ATP and shock application is visible via large stimulation artifacts. Durations of ATP and FFS were 630ms (black bars). Lower row shows the optical signal spectra during AT, ATP, and FFS. Spectra are shown in 0-30Hz windows. The spectrum of the signal during FFS shows a distinct additional peak at the frequency of the shock pulse train.

Conclusions ATP

1Mechanisms of ATP described in the textbooks are valid for 1 dim only

2 No systematic understanding of ATP mechanisms in 2dim and 3 dim exists, neither in experimental cardiology, nor in theory.

3 Theory predicts that ATP (a wave train) can eliminate a free rotating wave with100% success rate. 60-90% ATP success rate observed in experiments is an indication that rotating waves are pinned.

4. Far Field Pacing estimated to increase success rate of ATP for high frequency arrhythmias (where failure was induced by pinning or a large distance of the pacing electrode from the reentry)

5.Do you know other mechansims of ATP failure?
They may require other approaches.

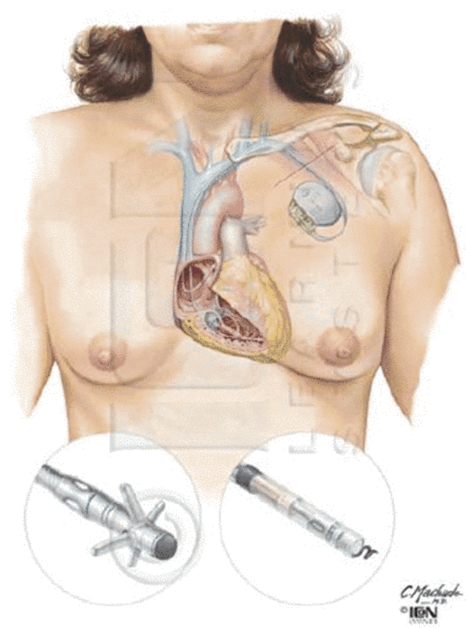
AF

Implantable pacemaker (IP)

Everybody knows that an Implantable Pacemaker (IP) is used to stimulate the heart when the natural pacemaker (SA) can't do it.

But an Implantable Pacemaker (IP) has also tools to terminate Atrial Fibrillation (AF).

Success rate is ~ 50%.

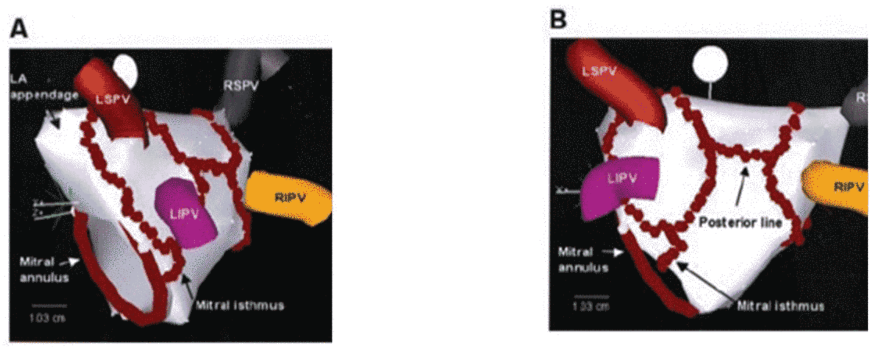


Atrial Fibrillation (AF)

It is clear what theoreticians can do for VF.

But what can we do for AF? It is not immediately dangerous for life.
Surgeons use Ablation to terminate AF, and it is efficient enough.

Ablation



These 3-D images of the heart's left atrium (white) and the pulmonary veins that connect to it (colors) show where U-M cardiologists delivered tiny radiofrequency 'zaps' in dotted lines to stop the irregular heartbeat patterns of atrial fibrillation patterns.
The procedure, called left atrial catheter ablation, cured the majority of AF sufferers in the newly released studies. Copyright: 2003 American Heart Association

AF: ablation 2006

Localized Sources Maintain AF Organized by Prior Ablation

Local radiofrequency ablation prolonged AF cycle length by 28±22 ms and either terminated AF
or changed activation sequence to another organized rhythm

Conclusions— AF associated with consistent atrial activation sequences after prior ablation emanates
mostly from localized sources that can be mapped and ablated.
Some sources harbor electrograms suggesting the presence of localized reentry.

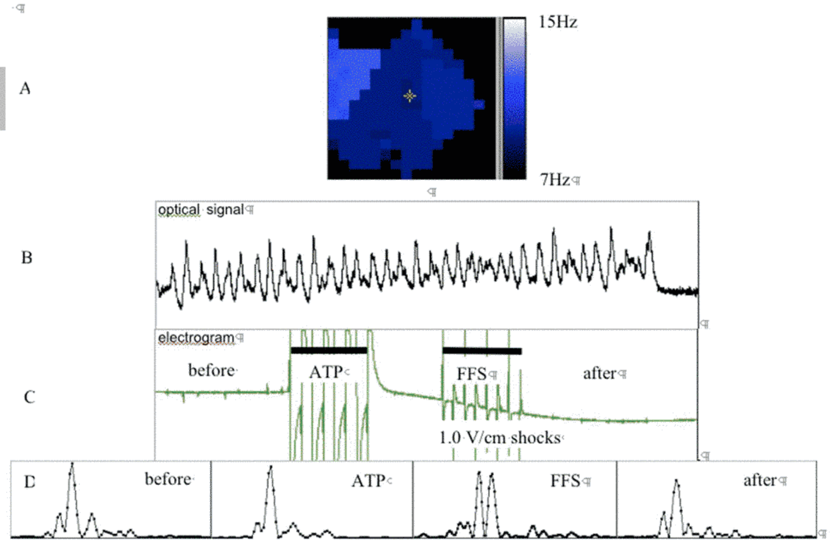
CIRCULATION 2006; 113: 616-625 Hassaguerre Michel, et al.

AF burden

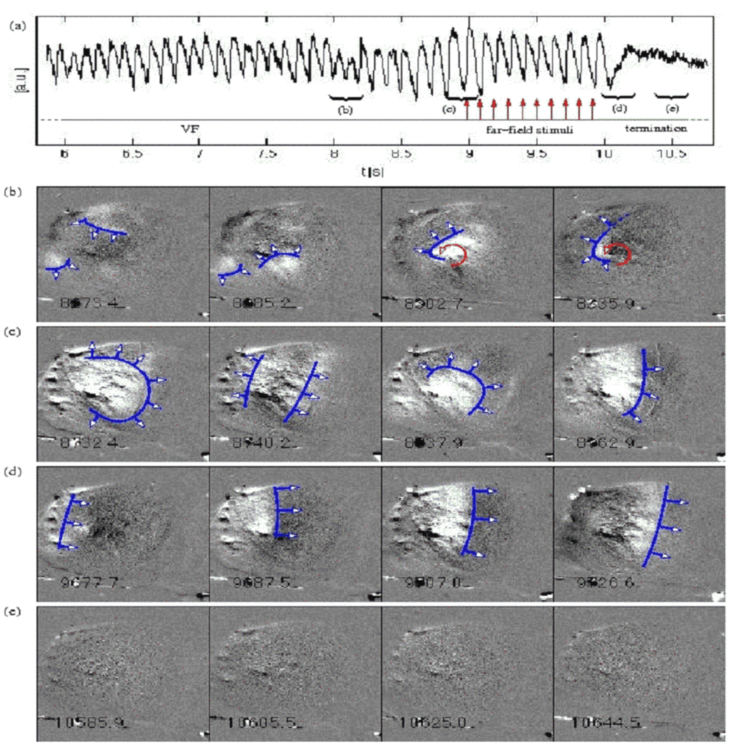
An answer found recently (my colleague Barelko got AF) is:

Physicists may help to decrease the AF burden,
(number of days where a patient has AF)

What other goals with AF could you propose? Welcome!!!



Rabbit heart . Termination of AF after Far-Field Stimulation (FFS).
A Š Map of the dominant frequencies across the right atrial free wall.
B - optical recording showing optical atrial action potentials during AF, ATP, FFS, and during post-stimulation termination. C - bipolar electrogram, recorded at the location of ATP electrode.. Durations of ATP and FFS were 630ms (black bars). D - optical signal spectra during AF, ATP, FFS, and during post-stimulation termination. Spectra are shown for 0-30Hz range. The spectrum of the signal during FFS shows a distinct additional peak at the frequency of the shock pulse train (Nikolski).



Canine heart.(Cornell Univ)
Successful termination of ventricular fibrillation (VF) by FFS (arrows).
10 stimuli 0.4 V/cm,
basic cycle length 100 ms,
pulse duration 5 ms.
(a) Time series from the optical recording.
(b) Irregular wave fronts during ventricular fibrillation.
(c) Wave interaction during onset of far-field stimulation.
(d) Periodic pacing and return to rest state.

Outlook: problems for future

In experiment, 20 times decrease of shock energy was demonstrated.

Now, it is time to develop physical approaches to ATP and AF.

Theoretical estimations of several paths permit to chose most effective ones. We started working on these probems theoretically and experimentally with

E. Bodenschatz, R.Gilmour, S. Luther, N.Otani.

We would be happy to invite other scientists join us.

Conclusions to the Talk

1. Far Electric Field provides a direct and not invasive access to an anatomical reentry circuit.
2. A weak shock from defibrillating electrodes creates membrane polarization around every anatomical obstacle. This polarization can serve to extinguish the arrhythmia if delivered in right time .
3. In experiment, 20 times decrease of shock energy was demonstarted.
4. Now, it is time for ATP and AF.
   Theoretical comparison of several paths permit to chose most effective ones for experiment. We started this work with Bodenschatz and Gilmour labs.

Conclusions 2

L.Tung's Grant on UnPinning

Grant Number: 1R21EB006171-01PI
Name: **TUNG, LESLIE**
Project Title:
Electrical Control of Reentrant Spiral Waves in Cardiac Tissue

Abstract: (provided by applicant):
...We hypothesize that there exists an optimal temporal window within the reentry cycle during which electric field pulses can successfully detach the wave.

Fiscal Year: 2006 Project Start: 01-APR-2006

End

We are thankful to KITP

Where we may freely exchange information,

Without being afraid that….

End