Biological Pacemakers

Moataz A. Zaki, MD

Lecturer of Cardiology - Medical Research Institute – Alexandria University.
Member -Editorial Board of Egyptian Cardiac Rhythm Association.
Fellow EP lab, Spedali Civili di Breschia, Italy.
M-EAPCI, M-EHFA

drmoatazzaki@yahoo.com

History of Bradyarrythmias

More than 2 millennia ago, Chinese physician Pien Ch'io reported what appear to have been heart block. He wrote that:

- "If 1 heartbeat of 50 were dropped, the patient was normal and had no diseased organs."
- "If the number increased to 1 in 40, then life expectancy was limited to 4 years, and a single organ was diseased."
- "As the number of dropped beats increased further, life expectancy diminished and diseased organs increased progressively."
- "At 1 dropped beat of 3 to 4, life expectancy was approximately a week."

Back to the Future

We now have achieved a pacemaker nirvana:

- AV sequential pacing permits the normal staging of atrial and ventricular contractions in patients with normal sinus nodes but with AV block.
- The coronary sinus permits access to the epicardial veins for biventricular pacing used in HF.
- ICDs that sense, shock, and pace when needed are life saving for patients with potentially lethal tachycardias.
- Units now being used can vary heart rate to adjust to the exercise level of a patient.
- Leadless electrodes are being developed that may permit stimulation of the heart without incorporating a catheter.

Drawbacks of electronic pacemakers

- Unresponsiveness to the autonomic nervous system (to the demands of exercise and emotion), although variable rate units are a potential answer to this need.
- Requirement for monitoring and maintenance, including battery or electrode replacement.
- Infection
- Interference from other devices ex: MRI.
- Risk of heart failure evolving with RV apical placement of electrodes (now being met by use of other electrode sites)
- Problems in adapting equipment to the growth and development of pediatric patients.

When can a Biological Pacemaker be superior to Electronic Pacemaker ?

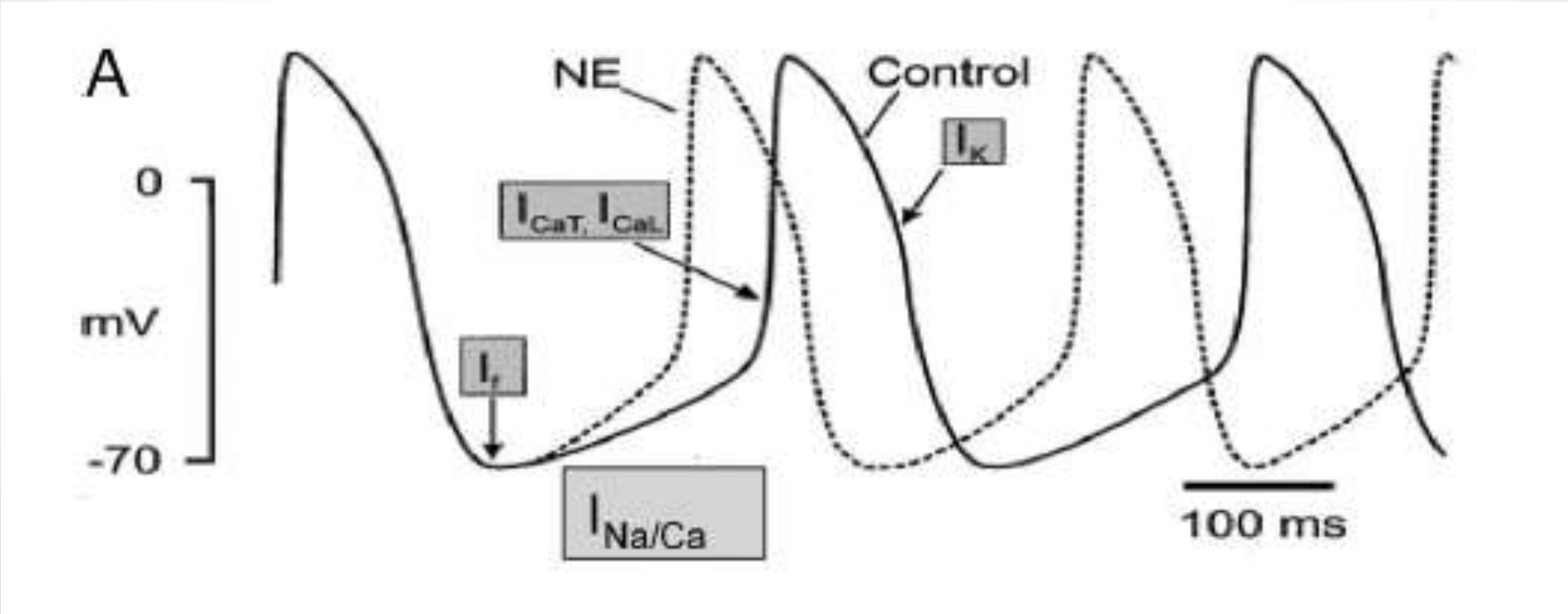
- If it competes effectively in head-to-head competition with electronic pacemakers yet requiring no battery, no electrodes, and no replacement.
- If not only creates a lifelong, stable physiological rhythm but is also responsive to the autonomic nervous system and as such to the demands of exercise and emotional status.
- If it Is implantable at a site that optimizes the pathway of cardiac activation, such that contraction and cardiac output are similarly optimized.
- If it does not induce proarrhythmia or carry concerns about inflammation, infection, or neoplasia.

In other words, the ultimate aim is to cure rather than merely palliate.

It is only by curing, that the biological unit can achieve superiority.

How is it done ?

How does a normal pacemaker cell work?



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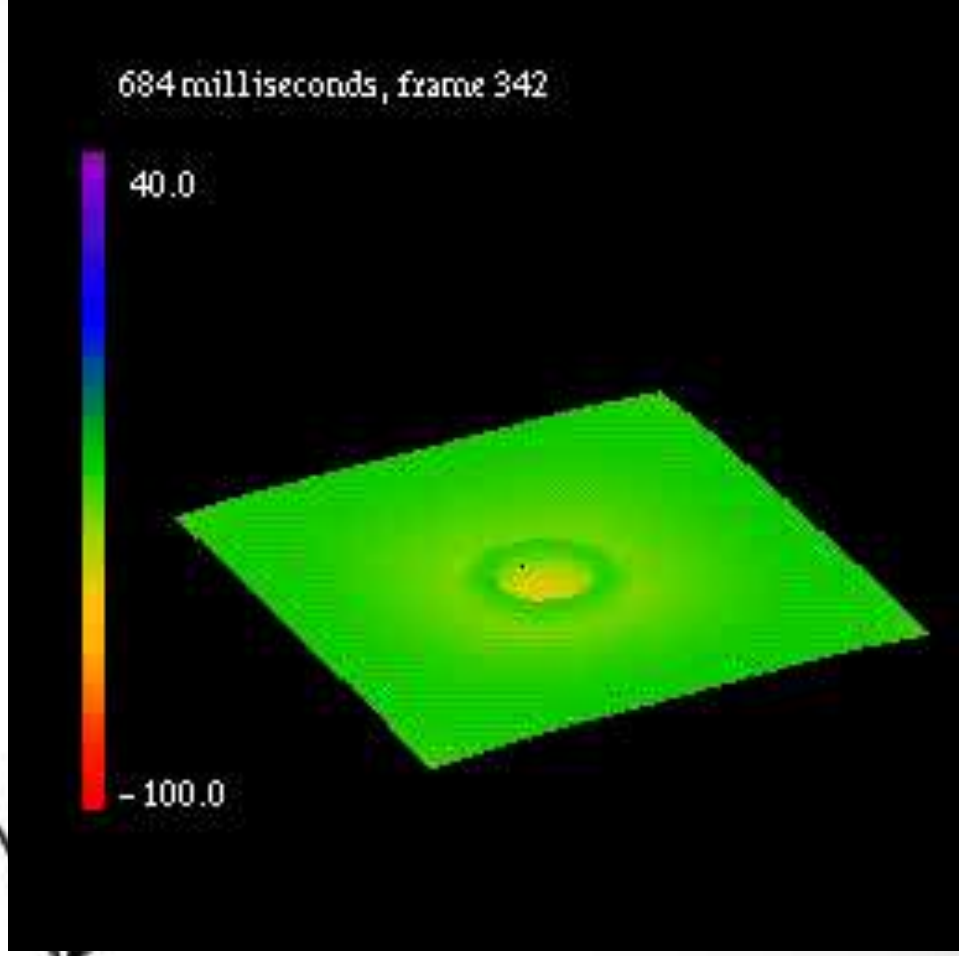

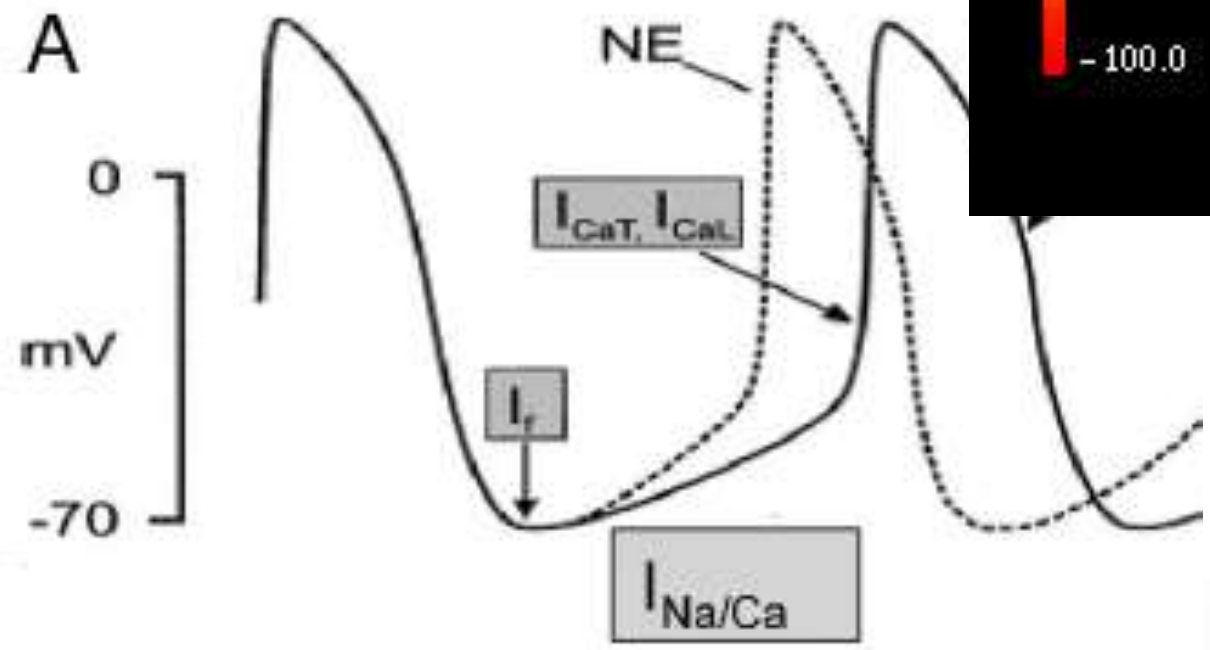

Strategies that have been used to generate biological pacemaker function are based on:

- **Gene Therapy**
- **Cell Therapy**

Gene Therapy

- Overexpress a gene that will increase pacemaker rate in cardiac myocytes (by increasing inward current)
- Knock out the function of a gene that would decrease pacemaker rate (and decrease outward current).

Gene Therapy

- The first biological pacemaker created was based on overexpression of 2-adrenergic receptors in porcine atrium.
- The result was an increase in basal atrial rate as well as responsiveness to catecholamines.
- While providing proof of concept that biological pacing might be workable, this approach carried the potential proarrhythmic complications of excess catecholamine action on the heart.

Gene Therapy

- The other ion channel approach that has been explored and largely adopted by most groups now working in the field is to increase or to create a variant on the inward current ***I*f [H**yperpolarization-activated **C**yclic **N**ucleotide-gated (**HCN**) channels**]**
- ***I*f (HCN)** channel opens on hyperpolarization of the membrane to admit inward Na current. The channel closes rapidly on depolarization.
- These characteristics of opening and closing of the channel avoid proarrhythmia because inward current is generated during phase 4 alone and not during phase 2 or 3 of repolarization.
- As a result, there is no action potential prolongation that might lead to proarrhythmia.

Gene Therapy

Two viral vectors have been used in the gene therapy experiments.

- The first is adenovirus, which is expressed episomally only and is useful for proof-of-concept studies lasting 2 to 4 weeks at most.
- The second is lentivirus, which is incorporated in cells genomically; although it is slow to express, it should be permanent in expression for the life of the cell.

Gene Therapy

- HCN2 in an adenoviral construct expressed well in atrium and ventricle.
- When injected into the left atrium, it generates pacemaker function that is sensitive to both catecholamines and vagal stimulation, increasing and decreasing the rate, respectively.
- Concern:
  - Viral vectors for gene therapy can carry various risks (with the greatest concern being the transmission of viral based diseases)

Cell Therapy

- One approach uses **h**uman **E**mbryonic **S**tem **C**ells (hESCs) that are placed in cell culture and "forced" into a pacemaker lineage.
- The other approach uses adult **h**uman **M**esenchymal **S**tem **C**ells (hMSCs) or other cell types as platforms for delivering HCN genes.

Cell Therapy
Human Embryonic Stem Cells

- hESCs delivered acceptable pacemaker function for several months when injected into the ventricles of pigs
- hESCs coupled with the myocytes such that the signal transfer from hESCs to the heart is robust.
- Concerns:
  - Need for immunosuppression (General problem with hESCs).
  - General concern that hESCs might evolve into:
    - Hostile cell type (including the possibility of neoplasia)
    - Cardiac cell that does not have good pacemaker function, such as a ventricular myocyte.

Cell Therapy
Human Mesenchymal Stem Cells

- As opposed to hESCs, the multipotent hMSCs do not have the necessary ion channel components to generate a cardiac action potential.
- Present, however, is a robust population of connexins (Cx43 and Cx40) that are the protein building blocks of gap junctions that provide the low-resistance pathways for current to flow among cells.
- These properties led to the hypothesis that:
  - hMSCs couple electrically to one another and to myocytes with great efficiency
  - Electroporation could be used to overexpress HCN2 in hMSCs (the cells loaded well, obviating the need for viral vectors)
  - An hMSC would be hyperpolarized by any repolarizing myocyte to which it is electrically coupled. This hyperpolarization would generate inward current that initiates depolarization and an action potential in the myocyte.
- In that way, the 2 cells would constitute a single functional unit, with the hMSC providing the depolarizing stimulus and the myocyte the action potential.

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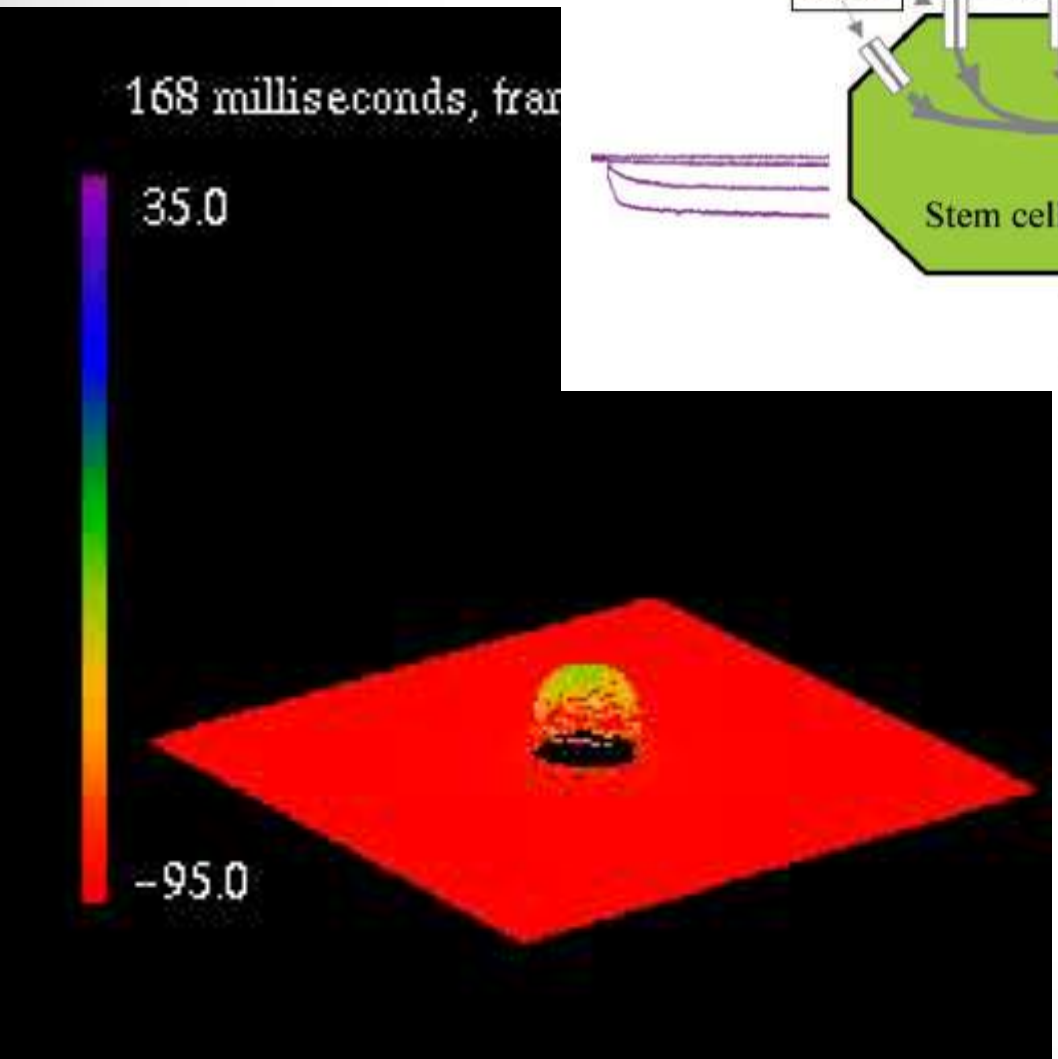

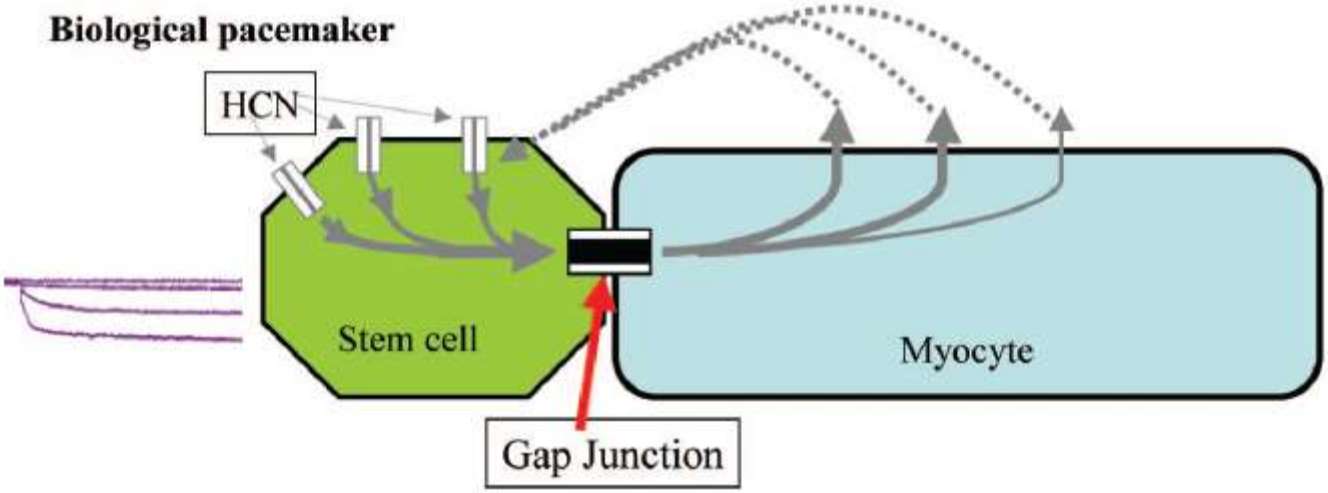

Cell Therapy
Human Mesenchymal Stem Cells

- hMSCs have been injected into the anterior left ventricular walls of dogs in complete heart block and have been studied through 6 weeks .
- Because there is evidence that hMSCs are immunoprivileged and are not necessarily rejected across species, these experiments were done without immunosuppression.
- The experiments were successful, showing pacemaker firing at 50 to 60 bpm in these animals as well as catecholamine responsiveness.
- Concerns:
  - Will they become a hostile cell type?
  - Will they stay in place or migrate elsewhere?
  - What will be their longevity when injected into the heart?

Where Do We Stand, and What Is the Future?

- The likely way to proceed clinically when ready would be to implant both a biological pacemaker and an electronic demand pacemaker in the same individual so called ***"Tandem Pacing"***.
- An adenoviral HCN2 construct was delivered in dogs together with an electronic demand pacemaker.
- The biological pacemaker fired 70% of the time and was catecholamine responsive.
- When the biological unit slowed, the electronic unit took over seamlessly.
- The electronic unit sensed the biological unit well and discontinued its function when the biological function emerged.

Where Do We Stand, and What Is the Future?

Extrapolating this tandem system to the clinic, one can envision a situation in which the biological pacemaker:

- Provides the majority of beats to the heart, conserving the battery of the electronic unit, and
- Is autonomically responsive, adding this component of function to the patient's heart.
- Via placement at a site in the conducting system that maximizes cardiac output, the biological unit provides another benefit not seen with electronics to date.
- At the same time, the memory function of the electronic unit can track the function of the biological unit, providing a record for the cardiologist.

Issues for the Future

- Whether the biological approach is in fact superior to the electronic pacemaker in terms of adaptability to the body's physiology and duration of effectiveness
- What is the Long-term incidence of:
  - Inflammation
  - Infection
  - Rejection
  - Neoplasia
  - Proarrhythmic potential
  - whether there is localization versus migration of the viral vector or cells administered
  - For stem cells, the persistence of administered cell types versus their differentiation into other cells.
  - Other toxicities, not yet conceived of, must be watched for
  - Delivery systems must be optimized.

Final Thoughts

- The biological approach does not arrive at a time when electronics are static. As mentioned earlier, rate responsiveness is here, and improved and leadless systems have arrived as well.
- Therefore, we see 2 competitive approaches evolving.
- Which one wins out is irrelevant.
- What is important is to identify the better approach and to bring it to the benefit of the patient .

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