A Promising Future – An Alternative to Electronic Pacemakers

By Hillary Kao

The human heart is a powerful, muscular pump. It contracts continuously to circulate oxygenated blood throughout the entire body.

The heart is comprised of 3-5 billion specialized cells called cardiomyocytes. Unlike most organs of the body, the heart is unable to regenerate itself if any of its cells are damaged, which often occurs as a result of cardiovascular diseases.

Cardiovascular disease can also cause arrhythmia, a term used to describe an abnormal heartbeat. Left untreated, arrhythmias can cause fainting, shortness of breath, damage to other organs, stroke, or sudden cardiac arrest. There are several different types of arrhythmia. One in particular is called sinus node dysfunction, where the heart's natural pacemaker generates an abnormally slow heart rhythm. This type of arrhythmia has a prevalence between 403 and 666 per million. Depending on the severity, doctors may treat such a condition by implanting an electronic pacemaker.

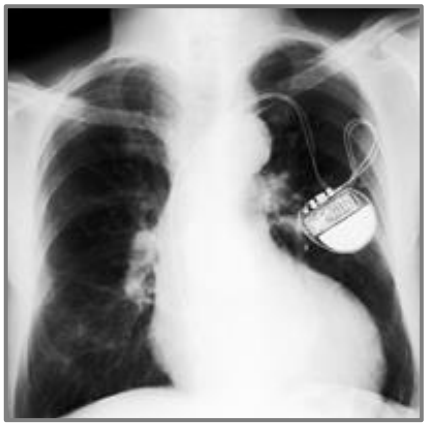

Figure 1. X-ray image of an electronic pacemaker

An electronic pacemaker is a small battery-operated device that generates electrical impulses, which are delivered through implant leads, to stimulate the heart to beat at a normal rhythm.

Although current pacemakers work quite well, they also have their limitations.

For instance, pacemaker implantation is expensive. The device itself is about $58,000, but also involves costly surgery and hospital stay.

Adding to the cost and inconvenience, pacemakers require ongoing maintenance. Invasive surgery is needed for battery replacement (every 5-12 years), in the event of lead failure, or for changing short leads in growing pediatric patients. Not to mention, pacemakers are susceptible to magnetic interference, which can disturb or deactivate its function.

Scientists working in the field of regenerative medicine are hopeful that their work will relegate pacemakers to ancient medical history. Regenerative medicine involves the use of stem cells to "regenerate" lost or damaged tissues. The most multi-faceted type of stem cell is the pluripotent

stem cell (PSC). “Pluripotent” refers to the ability of these stem cells to develop into any cell type within the body.

This defining property of PSCs qualifies them as candidates for a wide variety of research and potential therapies. However, their use has been controversial; human embryonic stem cells (hESCs) were the first identified source of PSCs. Many people object to the use of hESCs because the derivation process involves early stage human embryos.

In recent years, scientists have found a way to avoid using of hESCs by creating what is known as human induced pluripotent stem cells (hiPSCs). Scientists can generate hiPSCs by reprogramming normal skin cells. A few genes (that are usually found in the human egg cell) are added to the skin cells, which changes the skin cells into embryonic-like cells that are pluripotent and, therefore, have regenerative properties.

There are significant advantages to using hiPSCs in experimentation:

- They are relatively easy to generate.
- They behave similarly to hESCs in their ability to remodel themselves into any specialized cell-type.
- There are no ethical issues surrounding their use because human embryos are not used in the derivation process.
- Because hiPSCs can be made from a patient’s own skin cells, there are no issues with immune rejection.

Because of these advantages, many scientists within the field of regenerative medicine now prefer using hiPSCs.

One of these scientists is Dr. Deborah Lieu at the University of California, Davis – Institute for Regenerative Cures. She is using hiPSCs to make “pacemaking” heart cells to try to treat arrythmia. These specialized heart cells have the ability to control the beating of the heart. Dr. Lieu’s ultimate goal is to use hiPSC-derived pacemaking cells to create a “bio-pacemaker” that could serve as an alternative to current electronic pacemakers.

The first step is figuring out how to create pacemaker cells from hiPSC cells. To do this, Dr. Lieu’s research team must figure out how to mimic conditions within the human embryo that guide pacemaker heart cell development. They are doing this by adding specific cocktails of small molecules and cell culture media at exact time points to very precisely guide cell development.

Once the hiPSC-derived pacemaking heart cells reach maturity, Dr. Lieu and colleagues plan to examine them using different experimental analyses.

Thus far, most research in this area has focused largely on another type of heart cell called contractile heart cells, meaning there is still a lot to be learned about pacemaker cells before they can move from the laboratory to patient bedside.

Dr. Lieu's group will use microscopic analysis to examine cell shape and protein configuration inside the hiPSC-derived pacemaking heart cells and make comparisons to both normal pacemaker cells and contractile cells. They can also measure differences in what types of genes are expressed in these cells by quantifying the content of different proteins (which are coded for by genes).

It will be particularly critical to examine the electrical membrane potential, also called the action potential (AP), of the hiPSC-derived pacemaking heart cells. Pacemaker heart cells have a distinct AP that is different from other regions of the heart. If these hiPSC-derived cells are to be used therapeutically, it is essential that they retain the normal APs found in native pacemaker heart cells.

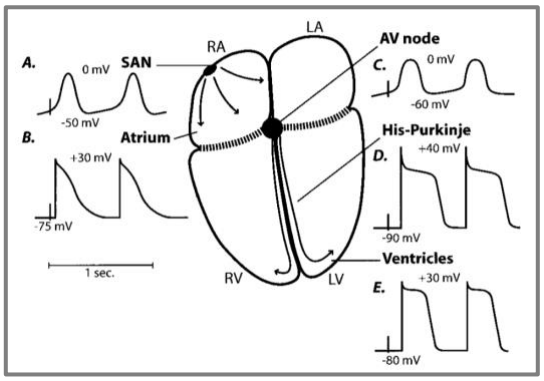

Figure 2. Diagram of action potential profiles of different regions of the heart. SAN (sinoatrial node) is the region comprised of pacemaker heart cells.

At present, Dr. Lieu and colleagues continue their research.

Once they have successfully generated hiPSC-derived pacemaking heart cells, they hope their research will be utilized for other applications, such as, drug toxicity testing, patient-specific hiPSCs for studying cardiac dysfunctions, and personalized medicine.

References:

Bergmann, O., Bhardwaj, R. D., Bernard, S., Zdunek, S., Barnabe-Heider, F., Walsh, S., . . . Frisen, J. (2009). Evidence for cardiomyocyte renewal in humans. *Science, 324*(5923), 98-102. doi:10.1126/science.1164680

Hyslop, L. A., Armstrong, L., Stojkovic, M., & Lako, M. (2005). Human embryonic stem cells: biology and clinical implications. *Expert Rev Mol Med, 7*(19), 1-21. doi:10.1017/S1462399405009804

Lieu, D. K., Fu, J. D., Chiamvimonvat, N., Tung, K. C., McNerney, G. P., Huser, T., . . . Li, R. A. (2013). Mechanism-based facilitated maturation of human pluripotent stem cell-derived cardiomyocytes. *Circ Arrhythm Electrophysiol, 6*(1), 191-201. doi:10.1161/CIRCEP.111.973420

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Turner, M. B. (2016). Heart disease and stroke statistics - 2016 update: a report from the American Heart Association. *Circulation, 133,* e38-e360. doi:10.1161/CIR.0000000000000350

Schram, G., Pourrier, M., Melnyk, P., & Nattel, S. (2002). Differential Distribution of Cardiac Ion Channel Expression as a Basis for Regional Specialization in Electrical Function. *Circulation Research, 90*(9), 939-950. doi:10.1161/01.res.0000018627.89528.6f

Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., & Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell, 131*(5), 861-872. doi:10.1016/j.cell.2007.11.019

Yamanaka, S. (2007). Strategies and new developments in the generation of patient-specific pluripotent stem cells. *Cell Stem Cell, 1*(1), 39-49. doi:10.1016/j.stem.2007.05.012