PHOL 519 – CARDIO-RESPIRATORY PHYSIOLOGY
Cardiovascular Control in Disease: Cardiac Arrhythmia
Feb. 28 and Mar. 2, 2017
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The autonomic nervous system plays an important role in the control of cardiac electrophysiology. Normal changes in autonomic tone can become pathogenic in a variety of inherited and acquired diseases that cause arrhythmia. In order to understand the complex interaction between cardiovascular control and arrhythmia, this week's classes will address molecular-, cellular-, and organ-level mechanisms of arrhythmia.

This week's sessions are as follows:

On Tuesday Feb. 28 I will lecture for 30 minutes followed by class discussion questions based on the required reading material (below). Students have been assigned one question for which they will be responsible for leading our discussion (also below). Every student should be prepared to contribute to every discussion question. Grading for this class session is based on presentation of your discussion question as well as participation in our discussion of other questions.

On Thursday Mar. 2 we will be reviewing 3 recent original research papers (below). For this session, I have divided you into 3 groups, with each group responsible for leading discussion on one of the three papers. Groups will very briefly discuss relevant background information to their assigned paper, followed by presentation of primary figures. You should divide figures amongst group members. Grading for this session will be based both on your assigned discussion material as well as your contribution to discussion of the other papers. Students should be prepared to contribute to the discussion of all 3 papers.

Reviews for the Feb. 28 Session:

1) Collingridge GL, Olsen RW, Peters J, and Spedding, M. 2001. Molecular and cellular mechanisms of cardiac arrhythmias. *Cell* 104:569-580.
2) Venetucci L, Denegri M, Napolitano C, Priori SG. 2012. Inherited calcium channelopathies in the pathophysiology of arrhythmias. *Nat. Rev. Cardiol.* 9:561-575.
3) Shen MJ, Choi EK, Tan AY, Lin SF, Fishbein MC, Chen LS, Chen PS. 2012. Neural mechanisms of atrial arrhythmias. *Nat. Rev. Cardiol.* 9:30-39.

Discussion Questions for the Feb. 28 Session: This discussion section will review the basic mechanisms underlying arrhythmias. The objective is to understand how proteins implicated in congenital arrhythmias function normally, and how their dysfunction leads to changes at the cellular level, which ultimately preclude organ level dysfunction. You should be prepared to discuss the following 8 questions in depth:

1. What is long-QT syndrome and how are congenital mutations in ion channels thought to contribute to long-QT?

2. Explain the concept of "reentry" and how molecular mechanisms lead to reentry and arrhythmias. Explain how "reentry" causes tachycardia.

3. Describe mechanisms thought to contribute to acquired arrhythmias, and some commonalities between congenital and acquired arrhythmias.

4. What is the multi-hit hypothesis for triggering arrhythmias, and what evidence is there for this hypothesis clinically?

5. Describe normal cardiac myocyte calcium handling and why spontaneous calcium release from the SR is potentially catastrophic.

6. Explain the molecular and cellular mechanisms underlying catecholaminergic triggering of arrhythmias.

7. Explain the organization of the cardiac ANS. What clinical and preclinical evidence demonstrates the role of the autonomic nervous system in generation or "trigger" of arrhythmias?

8. How could electrical stimulation of different aspects of the nervous system—central, peripheral, or cardiac—be used as a therapy for cardiac arrhythmias?

Research Papers for the Mar. 2 Session:

1) Vikram A, et al. 2017. Sirtuin 1 regulates cardiac electrical activity by deacetylating the cardiac sodium channel. *Nat. Med.* (**GROUP 1**)
2) Erickson JR, et al. 2013. Diabetic hyperglycaemia activates CaMKII and arrhythmias by *O*-linked glycosylation. *Nature* 502: 372-376. (**GROUP 2**)
3) Jungen C, et al. 2017. Disruption of cardiac cholinergic neurons enhances susceptibility to ventricular arrhythmias. *Nat. Comm.* 8:14155. (**GROUP 3**)