Jessica L. Slabaugh
PhD Candidate

“The Occurrence of Alternans and Arrhythmias in a Multicellular, Cardiac Preparation”

November 19, 2012
Hamilton Hall, Room 304
2:00 PM
VITA

2003-2007 ............................... B.S. Chemistry, Biology, Indiana Wesleyan University

2007-2012 ................................. Ph.D. Cellular and Molecular Physiology, The Ohio State University

COMMITTEE MEMBERS

Dr. Paul M. L. Janssen, Ph.D. Advisor

Dr. Mark T. Ziolo, Ph.D.

Dr. Sandor Gyorke, Ph. D.

Dr. Peter J. Reiser, Ph.D.

RECENT PUBLICATIONS


AWARDS AND HONORS

Nishikawara Service Award, The Ohio State University, March 2011.

Research Recognition Award, Department of Physiology and Cell Biology, The Ohio State University. December, 2010.

ABSTRACT

The cardiovascular system is an intricate structure responsible for a multitude of tasks; however, the primary function of the heart is to pump blood to the rest of the body. This pump is extremely important in maintaining cardiac output, and, for this reason, there are several regulatory mechanisms to modify contractility and preserve cardiac function. Although the contractile function of the heart is very well regulated, the normal pump apparatus and regulatory mechanisms often become dysfunctional, which can cause a multitude of pathological conditions. Therefore, our goal was to study the heart under conditions that alter several of these regulatory mechanisms in an effort to understand how the heart functions. In our studies we utilize a novel, multicellular approach where muscles are extracted from the ventricular free wall of the heart. These muscles allow us to manipulate and monitor both contractile function and calcium measurements. Our hope is to build a better understanding of how the healthy myocardium functions in an effort to understand the heart’s progression to disease.

The AP duration is extremely important in limiting the frequency of depolarization and allowing for proper relaxation of the ventricles. Without the support of the refractory period, the heart would be unable to sufficiently fill with blood and ventricular ejection would be reduced. To what extent the refractory period prevents successive APs to activate the ECC process and contractile machinery at supra-physiological rates, such as those present during ventricular fibrillation, was previously unknown. Therefore, in this particular aim we wanted to investigate the ability of the myocardium to contract at these high pacing rates. Utilizing multicellular trabeculae isolated from rat myocardium, we studied amplitude and kinetics of contraction at rates well above the normal in vivo rat heart range. We demonstrated that in rats, under high frequency conditions that are well above the normal heart rate, the isolated trabecula is able to twitch normally until 20 Hz. Therefore, the excitation-relaxation period in
trabeculae is short enough that under physiologically relevant conditions, mechanical alternans cannot occur. Alternans begin to appear at well beyond twice the maximal in vivo heart rate of the rat in approximately half of the muscles. We also saw similar results in mice, where the alternans appear at approximately twice the in vivo heart range. Therefore, our results suggest that even in the frequency-spectrum of ventricular fibrillation, which is roughly double the maximal heart rate, controlled and regular mechanical activity of the heart can be maintained. It is our hope, that through enhancing our understanding of the function of the heart as it pertains to frequency, we will be able to develop novel therapeutic techniques and identify targets for treatment.

Calcium is extremely important in maintaining proper function in the heart, and arrhythmias often occur when calcium is altered. When both the cytoplasmic and SR Ca2+ concentrations are increased, the open probability of the RyR2 is increased by the dissociation of CASQ2 from the RyR2 complex. As a result, Ca2+ waves are initiated and are often associated with triggered afterdepolarizations, which have the capability to initiate sustained arrhythmias. It is believed that some synchronization mechanism exists that has the ability to synchronize afterdepolarizations and APs in neighboring myocytes, possibly by similarly timed recovery of RyR2 from refractoriness and reaching the threshold for spontaneous Ca2+ release simultaneously. For that reason, we were interested in examining whether there is a synchronization mechanism for the generation of triggered activity in multicellular cardiac preparations. Utilizing multicellular trabeculae isolated from rat myocardium, we investigated the properties of these spontaneous Ca2+ waves by studying the contractile parameters and the Ca2+ dynamics in these muscles. We demonstrated that under conditions with both isoproterenol and caffeine, the cardiac trabeculae were able to synchronize their diastolic SR Ca2+ release. We also observed that we could visualize Ca2+ waves in the multicellular preparation with the addition of Rhod-2 AM. While these waves were not always present in every myocyte within the trabeculae, we were able to detect that, over time, the Ca2+ waves can synchronize in multiple myocytes. Since the diastolic Ca2+ release from the SR is the underlying molecular mechanism that ultimately causes afterdepolarizations and triggered arrhythmias, a better understanding of Ca2+ dynamics at the multicellular level is essential to expose the synchronization mechanism that occurs in the heart. This research will not only uncover the synchronization mechanism responsible for triggered arrhythmias, but will allow for the study of better anti-arrhythmic treatments in the future.

The results presented here provide evidence that even at extreme high frequency conditions that are well above the normal heart rate, both rat and mouse trabeculae are able to contract without developing arrhythmias or mechanical alternans. We, furthermore, show that diastolic SR Ca2+ release can synchronize in trabeculae. These findings suggest that both frequency and SR Ca2+ are important regulators of cardiac function in both health and disease. With further study, the results obtained here may help aid in the development of new therapeutic agents to treat alternans and arrhythmias.