IonOptix Platform and cardiomyocyte calcium handling

Plataforma IonOptix y manejo del calcio en cardiomiocitos

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Abstract

Excitation-contraction coupling is the basic calcium-mediated physiological regulation of cardiac contraction. It is critical for cardiac function, and its dysregulation is a key mechanism in heart disease pathology. This view describes the essential role of calcium management in cardiomyocytes and advances the IonOptix platform as an excellent ex vivo mechanism instrument of the above view in the mechanistic study. IonOptix allows for simultaneous, real-time assessment of intracellular Ca^{2+} transients and sarcomere shortening in single cardiomyocytes, allowing a complete functional reading of systolic and diastolic ratios. This reductionist approach is a powerful tool for identifying primary cellular pathophysiology, characterizing disease model phenotypes, and conducting drug screening. Here, we discuss its implementation in the Cardiovascular Physiology Laboratory at the Universidad de Valparaíso. We discuss the application to the Cardiovascular Physiology Laboratory of the University of Valparaíso, focused specifically on experimental models of diabetic cardiomyopathy and ischemia-reperfusion injury, as well as research collaboration that advances the understanding of new compounds with activity in the cardiovascular system.

Keywords: Excitation-Contraction Coupling, Cardiomyocyte Calcium Handling, IonOptix Platform, Diabetic Cardiomyopathy, Ischemia-Reperfusion Injury.

Resumen

El acoplamiento excitación-contracción es un proceso fundamental mediado por calcio que regula la contracción cardíaca. Su fina regulación es esencial para la función del corazón, mientras que su desregulación constituye un mecanismo central en el desarrollo de cardiopatías. Esta revisión describe el papel crucial del manejo del calcio en los cardiomiocitos e introduce la plataforma IonOptix como una herramienta ex vivo de primer nivel para su estudio mecanístico. IonOptix permite la medición simultánea y en tiempo real de los transitorios intracelulares de Ca^{2}+ y del acortamiento sarcomérico en cardiomiocitos individuales, ofreciendo

así una evaluación funcional integral de los parámetros sistólicos y diastólicos. Este enfoque reduccionista resulta eficaz para definir la fisiopatología celular primaria, caracterizar fenotipos en modelos de enfermedad y realizar.

Palabras clave: Acoplamiento excitación-contracción, manejo del calcio en cardiomiocitos, plataforma IonOptix, miocardiopatía diabética, lesión por isquemia-reperfusión.

Introducción

The basic Ca^{2+}-associated mechanism that mediates Ca^{2+}-related physical contraction of the heart muscle at the depolarization-to-mechanical contraction cycle is the excitation–contraction coupling and is established as follows excitation–contraction coupling (ECC) for cardiac muscle cells: (1) membrane depolarization and mechanical contraction. When ECC takes place, membrane depolarization triggers the relaxation of the voltage-gated L-type Ca^{2+} channels to allow for a small inward flow of the extracellular Ca^{2+}. This "trigger" Ca^{2+} activates ryanodine receptors (RyRs) on the sarcoplasmic reticulum (SR), and this releases a significant amount of stored Ca^{2+}, a process described as calcium-induced calcium release (2). The resulting rise in cytosolic Ca^{2+} triggers a contraction at the site of troponin C interaction, causing relaxation as the cytosolic Ca^{2+}moves into the SR much faster: the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA2a) pumps approximately ~70–90% of Ca^{2+} back into the SR, whereas the Na^{+}/Ca^{2+} exchanger (NCX) pumps the remainder away across the sarcolemma (3,4). As for cellular Ca^{2+} homeostasis, diastolic Ca^{2+} extrusion is supposed to precisely balance systolic influx.

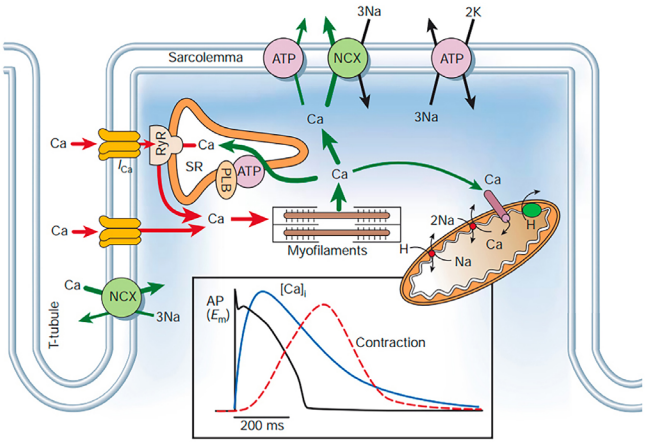

Figure 1. Ca_2+ transport in ventricular cardiomyocytes. The inset shows the time course of an action potential, a Ca_2+ transient, and sarcomere contraction. NCX: sodium-calcium exchanger; ATP: ATPase; PLB: phospholamban; SR: sarcoplasmic reticulum (1).

The IonOptix Platform

The IonOptix is now a gold standard platform for studying the ex vivo mechanism of cardiomyocyte ECC from a cardiomyocyte perspective. By controlling for Ca^{2+} cycling, IonOptix has been incorporated into CMA for the analysis of cardiomyocyte ECC and cardiovascular disease. Because the data is performed on the outside of the system in vivo environment of integrated environment beyond the human brain, including neurohumoral environment, mechanical stress-response, and multicellular networks such as multicellular interactions, it is powerful in its isolation of the cardiomyocyte's unique intrinsic properties (6). This focus on a reductive approach makes it very effective as an instrument in clarifying primary cellular pathophysiology as well as the effects of drug-free actions. The system relies on real-time, simultaneous measurement of intracellular Ca^{2+} transients (fluorescence-based indicators such as Fura-2) and sarcomere

shortening/re-lengthening in an individual living cell (Figure 2). Core functional parameters collected from these recordings are: Systolic function: Peak Ca^{2+} amplitude, contraction amplitude, and maximum rise rate. Diastolic function: At rest Ca^{2+} level and diastolic sarcomere length. Kinetic parameters: Time-to-peak and time to 50%/90% decay (tau), which describe the kinetics of SR Ca^{2+} release and reuptake.

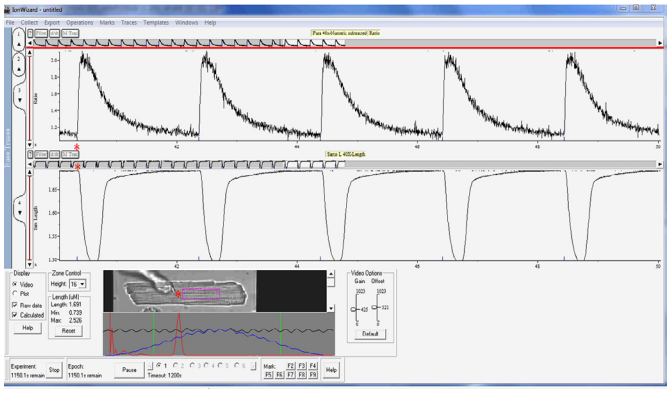

Figure 2. Simultaneous recording of intracellular calcium transients (top) and sarcomere shortening (middle) in a paced isolated cardiomyocyte (bottom). Red asterisks denote electrical stimuli applied to the paced cardiomyocyte (bottom).

This integrated functional readout makes IonOptix's integrated functional reading into an integrated report of the molecular pathway is what allows it to drive immediate causative links between molecular changes in proteins in functional aspects (as in protein expression, phosphorylation or genetic mutation, or genetic changes) and the functional consequence of such changes. Therefore, it is necessary for phenotyping diseases such as heart failure, hypertrophic cardiomyopathy, and diabetic cardiomyopathy and atrial fibrillation disease in models as well as drug phenotyping, as well as preclinical cardiotoxicity treatment based on a drug's use for drug screening is to say the least.

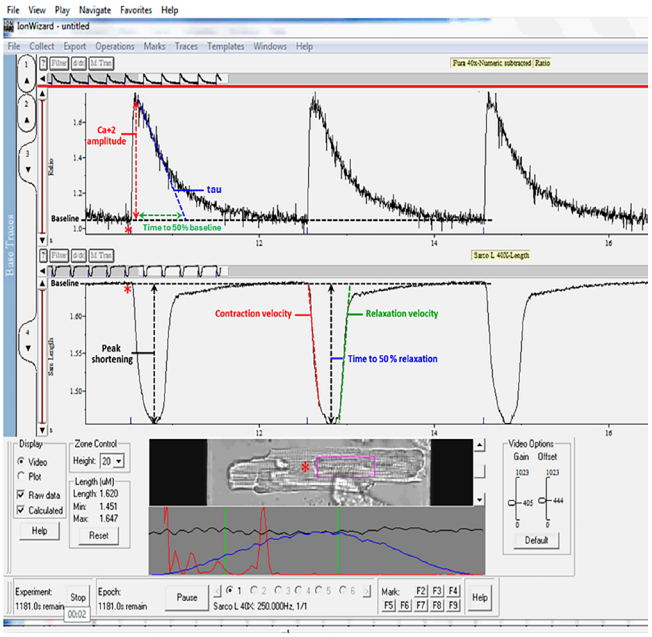

Figure 3. Calcium transient analysis (top). The black dashed line indicates the baseline fluorescence. The red dashed line with double arrows marks the peak calcium amplitude. The blue dashed line denotes the time constant of decay (tau). The green dashed line with double arrows indicates the time from peak to 50% decline. Sarcomere shortening kinetics (middle). The black dashed line with double arrows marks the peak fractional shortening. The red dashed line denotes the maximum velocity of shortening and the dashed green line the maximum velocity of re-lengthening and the time from peak shortening to 50% relaxation (blue line). These measurements were triggered by electrical field stimulation (red asterisks) applied to the paced cardiomyocyte (bottom).

IonOptix in the Cardiovascular Physiology Laboratory (LFCV)

The IonOptix platform within the LFCV (Department of Internal Medicine, Universidad de Valparaíso), where we have been providing analysis of ECC in experimental models of diabetic cardiomyopathy and hypoxia-reoxygenation — hypoxia modeling ischemia-reperfusion (I-R) injury of acute myocardial infarction (Figure 4). Since October 2023, we have co-developed I-R studies with the Department of Physiology at the Mayo Clinic (Rochester, MN, USA) (7,8) (Figure 5). We collaborated with Arturo Prat University of Iquique to investigate cardioprotective effects of oxime OxSn-IV from S. nutans. OxSn-IV is a perennial shrub from the high Andes used in experimental studies for combating altitude sickness, producing an oxime known to lower blood pressure. Figure 6 displays a representative work-flow experiment using IonOptix platform.

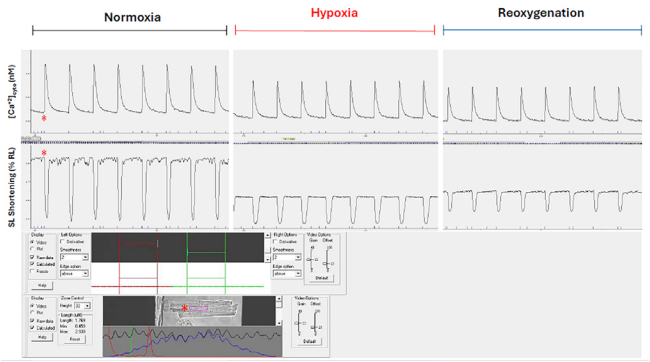

Figure 4. Representative tracings of calcium transients (top row) and sarcomere shortening (middle row) acquired simultaneously in an isolated cardiomyocyte (bottom row) after electrical stimulation (red asterisks). Data show the response to 15 minutes of normoxia, 15 minutes of hypoxia, and 15 minutes of reoxygenation (left to right columns). Hypoxia induced a reduction in calcium transient amplitude and a marked decrease in sarcomere shortening. Notably, this impairment was more pronounced during the reoxygenation period, demonstrating a failure of excitation–contraction coupling to recover.

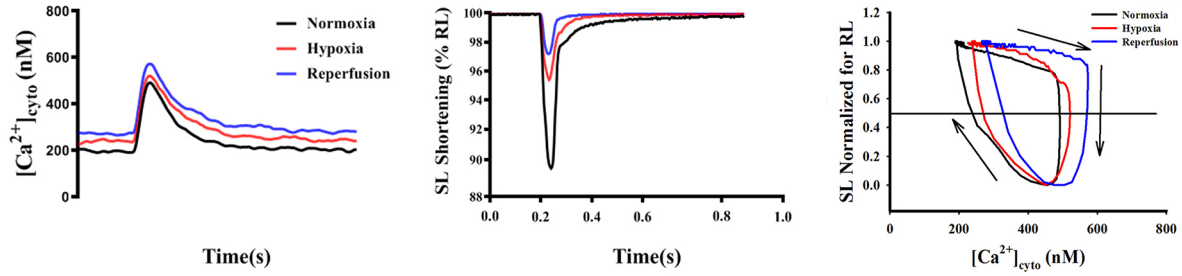

Figure 5. Graphical representation of simultaneous measurements (on the IonOptix platform) of calcium transients (left) and sarcomere length shortening (center) during 30 minutes of normoxia (black curve), 30 minutes of hypoxia (red curve), and 30 minutes of reoxygenation (blue curve). During the hypoxic period, no changes in calcium transients were observed, but a reduction in sarcomere shortening was noted. On the right, a phase-loop analysis illustrates the calcium sensitivity of the myofilaments. Here, calcium transients are plotted against sarcomere shortening—normalized to resting length—following electrical stimulation. Hypoxia induces a rightward shift of the loop along the calcium axis, an effect that becomes more pronounced during reoxygenation. This shift indicates that more calcium is required to achieve a given level of sarcomere shortening. In other words, hypoxia and subsequent reoxygenation impair excitation–contraction coupling in cardiomyocytes by reducing the calcium sensitivity of contraction (8).

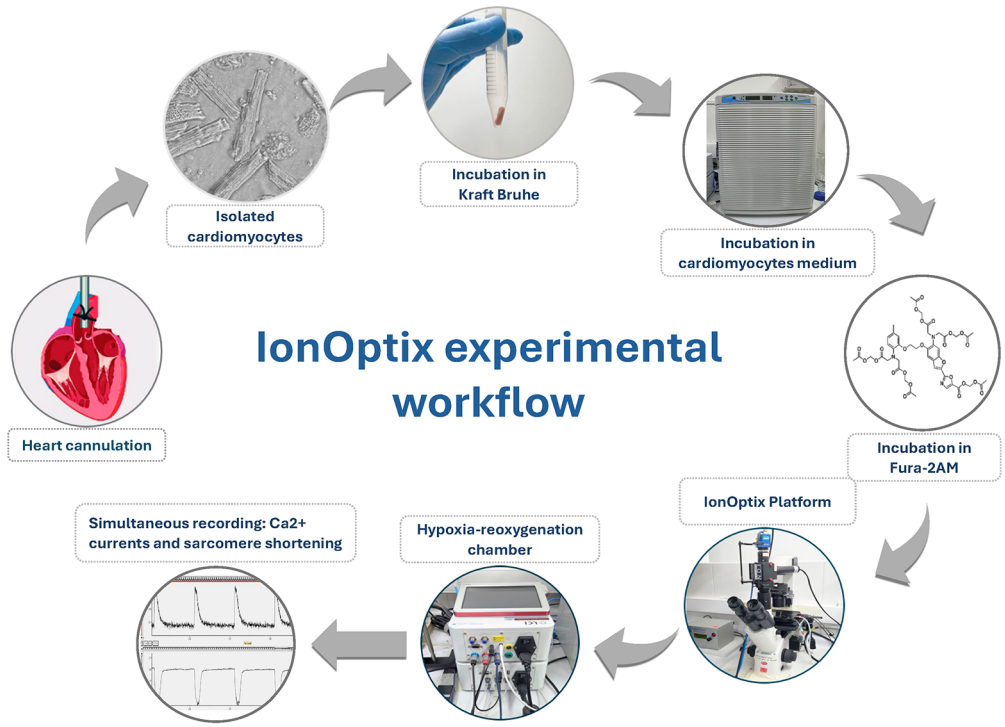

Figure 6. Schematic of the Experimental Workflow for IonOptix ased Assessment of Excitation-Contraction Coupling.

In summary, in our lab, the IonOptix platform is used in interdisciplinary research on metabolic diseases, hypoxia-reoxygenation studies, and cardioprotection from traditional medicine, clearly illustrating its importance in cardiovascular pathology research. Thus, IonOptix ensures understanding basic biology and accelerating drug discovery at the preclinical level.

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