SPECIAL EDITION

MINI INTERVIEWS

Physiological Mini Reviews

VOLUME 14
NUMBER 1

Foto de Edward Jenner en Pexels

Special Issue Vol 14 Nº1

http://www.pmr.safisiol.org.ar/

Physiological Mini Reviews

Physiological Mini-Reviews

[ISSN 1669-5410 (Online)]

Edited by **the Argentinean Physiological Society and the Latin American Association of Physiological Sciences**

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Physiological Mini-Reviews is a scientific journal, publishing brief reviews on "hot" topics in Physiology. The scope is quite broad, going from "Molecular Physiology" to "Integrated Physiological Systems". As indicated by our title it is not our intention to publish exhaustive and complete reviews. We ask to the authors concise and updated descriptions of the "state of the art" in a specific topic. Innovative and thought-provoking ideas are welcome.

Preparation and Submission of manuscripts:

"Physiological Mini-Reviews" will have a maximum of 3000 words, 50 references and 3 figures. Material will be addressed to scientific people in general but not restricted to specialist of the field. For citations in the text please refer to Instructions in our webpage. Final format will be given at the Editorial Office. Most contributions will be invited ones, but spontaneous presentations are welcome. Send your manuscript in Word format (.doc or .docx) to: pmr@safisiol.org.ar

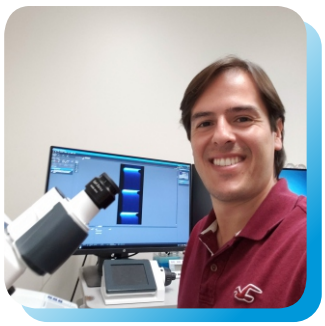
Dear colleagues:

We are happy to announce a new section in Physiological Mini Reviews.

The section is called Mini Interviews, and its purpose is to highlight the work of the first author (that are usually young investigators), of some of the already published Physiological Mini Reviews.

We believe that this initiative will further enrich the content of the journal and will contribute to promote and support researchers in the earliest stages of their careers.

Besides, publishing their experience, achievements, doubts and even failures, may also provide useful insights or even inspiration to other young people who are in a similar position.)



Mini Interview to Francisco Alvarado

••How did you become interested in science and, in particular, in research related to cardiovascular physiology?

Since I was a kid, I have had a predisposition for science, especially for biology and mathematics. I always wanted to be a doctor, as most kids do; however, my journey to cardiovascular research spans into adulthood.

I became interested in the medical field and cardiology as a teenager after my father was diagnosed with heart disease. I went with my parents to the medical appointments and tried to comprehend the nature of the disease and his condition. While the details escaped much of my understanding, I certainly realized the importance of a healthy heart – something I continue to think about almost every day. The concept of cardiovascular physiology came to my attention when I took a human physiology class in college. I was amazed by the idea that the heart does not need external inputs to beat and, given the right conditions, it can continue contracting ex vivo. The experiment with a Langendorff perfused mouse heart – an explanted beating heart mounted on a perfusion apparatus – was just mesmerizing. When I tell this anecdote my neurophysiologist friends are quick to point out that they can keep brain slices alive and neurons firing for hours on a dish. Well, yes, I reply, but you can see and feel the heart performing the work that keeps you alive. Beat that!

After graduation from college, I worked as a lecturer at the University of Costa Rica and I became involved in research on bacteriology and pharmacology. At the time there were no groups doing research on cardiovascular physiology at the institution, but my interest lingered and developed roots. I finally entered the field in graduate school when I joined Dr. Héctor Valdivia's lab at the University of Wisconsin-Madison. As a mentor, Héctor motivated me to cultivate a general interest in the heart into a passion to understand the intricate mechanisms regulating cardiac function and excitation-contraction coupling.

• ·What do you consider to be your substantial scientific contribution so far (provide Pubmed PMID if possible)?

I consider two papers where I am the first author to be my most substantial contribution so far. One deals with the regulation of the cardiac ryanodine receptor (RyR2) by phosphorylation at the residue S2808 (PMID 28065668). This is a controversial topic that I have continued to work on, trying to address different aspects of the problem – for example, are there other phosphorylation sites and what are their physiological relevance? The second describes an interesting mutation in RyR2, P1124L, found in a patient with hypertrophic cardiomyopathy (HCM) (PMID 30835254). The novelty about this mutation is that it is one of the first to be associated with structural remodeling of the heart, something we also observed in the moue model, when most mutations before were only related to cardiac arrhythmia.

I am also very proud of the collaborative articles to which I have contributed, particularly two studies from Dr. Mario Delmar's lab (PMIDs 31315456 and 28740174) that are shaping my current research.

• ·Which is your current research and the most exciting questions you find in your field?

My current research focuses on the regulation of calcium homeostasis in the heart. I am trying to understand how dysfunctional calcium release in various disease conditions predisposes or triggers structural remodeling of the heart and severe arrhythmias potentially leading to sudden death. With this knowledge, it can be possible to develop therapeutic strategies that can improve the life of patients. I currently apply these concepts to two specific inherited diseases: catecholaminergic polymorphic ventricular tachycardia (CPVT) and arrhythmogenic right ventricular cardiomyopathy (ARVC).

There are many exciting questions in the field. A popular one nowadays is how to improve the maturation of cardiomyocytes derived from induced pluripotent stem cells to potentially use in cardiac regeneration or as in vitro tools to study heart disease. Perhaps an even more exciting question is how cellular functions are regulated at the nanoscale in cardiac myocytes. To this day, I continue to be amazed that calcium is a second messenger involved in a myriad of processes, even cell death, and yet cardiomyocytes understand the nuance between the signal that triggers contraction and others that regulate signaling pathways. Compartmentalization of the cell into micro and even nanodomains is a fresh new perspective to answer this question.

·• Where do your research strengths lie? Why? What are your research weaknesses? How will you improve them, if any?

One of my weaknesses is that I tend to think a lot about calcium in the heart and sometimes frame scientific questions and hypotheses solely in terms of how a certain phenomenon affects calcium dynamics. This is unconscious, while at the same time I make a conscious effort to

expand my viewpoint. I attend seminars on varied topics, try to follow the general literature, and talk to investigators in areas that complement my research but lie outside my area of expertise. I try to pay more attention to other ion channels, signaling pathways, and techniques that can broaden not only my perspective of the field but also my research approach.

I think the two biggest strengths a scientist can have are open mindedness and objectivity. I can't claim these are my biggest strengths, although they are something I continually strive for. That, I think is my biggest strength: a strong need for improvement and to challenge myself. Furthermore, I am meticulous in my experiments and am very competitive, which help keep enthusiasm high.

•• Describe your unforgettable or proudest moment in science, and the most challenging situation that you have had to overcome (lessons learnt) so far?

The two proudest moments I have had were defending my doctoral thesis and obtaining my first research grant. These are critical milestones in the scientific career that, even as time goes by, continue to give me motivation. I hope that, as my career progresses there will be moments on par with these.

The most challenging situation I have had to overcome was when I was a PhD student. While troubleshooting an experiment, I realized that one of my projects was built upon the incorrect characterization of an animal model. This meant that most of the experiments I had performed so far would need to be repeated after the model was correctly characterized. The biggest lesson I learned is summarized in the Russian proverb “trust but verify:” trust your colleagues but verify together that all data are correct. After all, rigor and reproducibility are the corner stones of scientific progress.

•• Which was the first relevant conference where you presented? How was your experience?

As I was finishing my PhD at the University of Michigan in 2017, Dr. Alicia Mattiazzi invited me to present in a symposium at the 38th World Congress of the International Union of Physiological Sciences in Brazil. I had participated in many conferences before, huge ones like the American Heart Association Scientific Sessions and smaller but intense ones such as a Gordon Conference, but this was the first time I would deliver an oral presentation on the “big stage;” I was the only junior investigator presenting in the session. The other speakers were renowned investigators with prosperous careers, who shared impressive stories compiled from data gathered over many years, longer than I had been involved in research. Of course, I was nervous to step up to the podium to share one of my small projects. I was particularly worried about the questions, wondering what all the experienced investigators in the room would ask. Probably something I had not thought about. There were, indeed, a couple of difficult questions that I struggled to answer, but it was a wonderful experience! This presentation gave me the

opportunity to have a thoughtful discussion with experts at a level that was new for me. I continue to be in contact with many of the people I met at that conference and I thank Alicia for giving me such a great opportunity.

•• What is next for you and what are your scientific goals?

As an early-career investigator, my biggest goal is to establish my own independent research program and become a tenured professor in cardiac physiology. This means securing independent funding and publishing high impact articles, which are the short-term goals steering my journey. My first fully independent research project is under review right now. Hopefully, it will be a solid steppingstone towards my goal.

From a scientific perspective, my goal is to contribute to the understanding of how the heart works as well as how to prevent and cure disease. Carving a research niche within this broad goal and obtaining recognition in the field is not easy! In an interview with Circulation Research, Don Bers talks about how junior investigators usually struggle to establish a name of their own. I conscientiously follow his advice: to embrace hard work and patience.

•• Do you have any advice for emerging scientists?

Well, I am still an emerging scientist and I continually seek advice to succeed. The best I can think of is that having good mentors and collaborators, who are honest and constructive, gives you a substantial competitive advantage. So, choose your mentors and collaborators carefully! There are also a couple of important things I have come to appreciate.

First, perseverance is crucial. There will be moments when the experiments go smoothly, all the pieces of your research puzzle fit together, you come across exciting new ideas everywhere, and funding is plenty. But you must be prepared for the moments when things get difficult – funding is running low, papers are rejected, experiments fail. Taking a step back and looking at the big picture is the best way to keep things in perspective. Overall, having a hard skin for criticism, which in science is almost always constructive, keeping a positive attitude, and persevering are qualities of great value.

Second, a balanced life helps prevent burn out and increases productivity. Evidently the right balance is different for every person and there is no secret recipe. However, this can be difficult to achieve when the pace of scientific discovery is relentless. Someone once told me that it is impossible to succeed in science with an 8-to-5 Monday-through-Friday work schedule. I agree and simply add that caring for your mental health and having a balance that includes sufficient time off is as important to succeed as giving your greatest effort in the lab. Life balance helps increase productivity and clear your mind to make room for new ideas – perhaps the one that will become your next great paper or grant.

Finally, I want to mention a paper that made a big impression on me when I was a recent graduate from pharmacy school teaching at the University of Costa Rica and daydreaming about going to graduate school: “Ten simple rules for aspiring scientists in a low-income country” (PMID: 18437198), by Edgardo Moreno and José María Gutiérrez from the University of Costa Rica. It contains great advice for scientists who, like me, come from developing nations, but many points are more generally applicable to scientists everywhere.

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