

## **Electrophysiological remodeling of the pulmonary vein sleeve myocytes underpins atrial fibrillation in a canine model of long-term high intensity endurance training**

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### **Background:**

In humans, pulmonary veins (PVs) are four large vessels that deliver blood enriched in oxygen from lung lobes to left atrium (LA) of the heart. PVs harbor a particular subtype of myocytes (PV sleeve myocytes), which show unique electrical properties including automaticity [1]. It has been documented that the junctional area between the LA posterior wall and the PV ostium (LA-PV junction) is a key source of ectopic foci, which are electrical triggers, that can initiate and maintain atrial fibrillation (AF) [2]. AF is the most frequent cardiac arrhythmia worldwide and its incidence is forecasted to increase in the next decades. AF is a complex and multifactorial disease of the atrial rhythm, depending from several risk factors, including genetic heritage, cardiovascular disease, drug misuse, ageing and lifestyle. This complexity precludes successfulness of single-therapy approach. Thus, there exists high interest in defining the mechanisms underlying AF origin and recurrence in specific cohorts of patients to develop personalized therapeutic strategies. In this context, while clinical studies point toward increased incidence and up to five-fold risk of AF in endurance athletes [3], the mechanisms underlying association between chronic high-intensity training regimen and AF are not understood. In this study, we hypothesized that electrophysiological remodeling of pulmonary veins accompanies long-term high intensity endurance training and such remodeling accompanies increased susceptibility to AF onset in trained cohorts.

### **Aim:**

To study electrophysiological remodeling of pulmonary veins in a canine model of training-induced atrial fibrillation.

### **Scientific experience:**

I arrived in Szeged at the end of dogs training period and animals were ready for electrophysiological studies. Especially, trained dogs were subjected to 4 months of treadmill (TM) exercise (ExT, running for 80 kms per day) [4].

Trained by Dr. Luca Soattin, from Alicia D'Souza Lab and helped by collaborators from András Varró Lab, I had the opportunity to perform multielectrode array mapping in intact animal. During this unique experience, I acquired signals derived from PV region in ExT dogs and I compared them to age-matched sedentary dogs (Sed). Results documented increased AF incidence and duration in PVs from trained vs sedentary dogs as well as increased incidence of spontaneous ectopic beats that propagated to the atria.

### **Conclusions:**

These data support the hypothesis that there is training-induced electrical remodeling of the PV sleeve myocytes. This is the first indication of training-induced remodeling of the PVs in a large animal model providing translational insights into the electro-anatomical PV-substrate predisposing athletes to AF.

### **Future perspectives:**

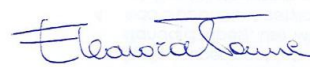
This grant has given me the unique opportunity to perform invasive electrophysiological study in large animals. I have harvested tissues from the pulmonary vein from trained and sedentary groups and in collaboration with Alicia D'Souza I will analyse the PV ion channel and epigenetic profile to further explore the mechanistic basis of heightened AF susceptibility in athletes. A high-impact publication is anticipated from this work. Moreover, this exchange also allowed me to build strong collaborations and connections with the University of Szeged.

### **Acknowledgments:**

I would like to thank Dr. Alicia D'Souza, Professor András Varró and Professor István Baczkó to give me the possibility to be part of this project. I am also very thankful to Luca Soattin and all of the collaborators in Szeged that - in addition to support me scientifically - made me feel at home. Finally, I am grateful to the European Working Group in Cardiac Cellular Electrophysiology for supporting this exchange.



**Professor István Baczkó**  
Director of the host institution



**Eleonora Torre**  
Exchange grant awardee

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