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Scientific abstract – *Atrial fibrillation substrate induced by a chronic atrial implant in the small mammalian heart: pathophysiological mechanisms and clinical implications*

Atrial fibrillation (AF) is a medical challenge with for substantial economic costs, morbidity and mortality. AF has a complex and progressive nature and is associated with multiple risk factors and changes in the tissue (atrial remodeling, AR), many of which remain elusive. Manipulations aimed at inhibiting AR are considered attractive new strategies against AF. Enhanced mechanical loading (ML) is presumably an important detrimental factor leading to AR. ML is present either in conditions generating primary atrial overload or when ventricular overload is transmitted in a retrograde fashion to the atria. As in the ventricles, the atrial response to ML has pathological consequences. The readily available models for studying this complex process are limited. While rodent models are important, and their use in AF research has grown exponentially over the last two decades, they are limited by multiple technical considerations. Our laboratory has developed an implanted system with a unique quadripolar electrode adapted for advanced atrial electrophysiology (EP) studies in freely-moving small mammals (rats and guinea pigs) over time. Moreover, we recently succeeded in developing an unbiased algorithm to accurately access the complexity of AF episodes as part of the AF analysis. A remarkable and consistent finding that we identified by following rats with atrial implants over time is the progressive development of AR characterized by atrial refractoriness (AERP) shortening and rise in the AF susceptibility. After excluding several possibilities, we *hypothesize* that AR induced by the atrial implant is related to ML and pathological hypertrophy of the affected tissue. To address this possibility in detail, our first objective will be to directly demonstrate that the atrial implant induces AERP dispersion between the loaded and normal atrial tissues. This will be leveraged by our ability to measure AERP in both atria following extraction of the heart with the implant and reconnecting it to an *ex vivo* EP setup. Our second objective will focus on delineating early molecular and biochemical changes in the loaded atria as well as morphological and functional changes in acutely isolated cardiomyocytes from chronically implanted atria. Finally, we will explore the ability of promising therapeutic manipulation to attenuate AR induced by the implant. These manipulations will include: a) anti-hypertrophic AAV9-based manipulations of mAKAPβ signalosome-regulated serum responsive factor (SRF) phosphorylation, a recently identified critical hypertrophic switch; b) the effect of the widely used anti-inflammatory medication colchicine, found to be useful for AF prevention in several specific settings; and c) a new SK4 channel blocker (BA6b9), with important anti-fibrotic and anti-AF properties according to our preliminary findings. Overall, our goal is to establish implant-induced atrial hypertrophy as a first targeted and readily available experimental model for specific studies of atrial ML and to contribute new insight, at the molecular level, of the pathological consequences of atrial hypertrophy as a drug target in the combat against AF progression.