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Atrial electrophysiological properties in different species compared to patients – Is there a perfect atrial animal model?

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Background:

Atrial rhythm disorders – ranging from atrial fibrillation (AF) as a widespread disease over the development of arrhythmias in the context of heart failure or genetic syndromes to postoperative AF – constitute a heterogeneous group of diseases, with high relevance for individual patients as well as the whole health care system. There is an urgent need for developing new specific treatment options to restore and maintain normal heart rhythm. Therefore, it is crucial to gain a better understanding of atrial electrophysiological properties in a (patho-)physiological context, for which different animal models play an important role. Still, specifically for the atria, differences in electrical properties between human and animal species commonly used in cardiovascular research have never been characterized systematically.

Purpose:

We aimed to elucidate atrial electrophysiological differences between patients and relevant animal species on a cellular electrophysiological, morphological, transcriptomic as well as clinical level, to identify problems for translation as well as opportunities for improving preclinical models.

Methods:

For cellular electrophysiological studies, cardiomyocytes (CMs) were isolated from atrial samples of sinus rhythm (SR) patients undergoing open heart surgery. At the same time, right and left atrial tissue was harvested from mice, rats, pigs and horses in SR. Evoked action potentials (APs) were measured from isolated CMs using the patch-clamp technique and measured CMs were then also characterized morphologically. Regarding transcriptomic analyses, we have developed a method to compare atrial ion channel expression profiles calculated from RNA sequencing datasets of the different species. Further, we also investigated differences in P-wave characteristics between surface ECGs of patients, pigs and horses.

Results:

For mouse and rat CMs we observed significantly lower AP amplitudes and upstroke velocities, compared to human, porcine and equine cells. Interestingly, AP durations (APDs) increased from mouse over rat and pig to equine CMs. The APD at 90% repolarization (APD_{90}) of human atrial APs was significantly shorter than in horses and ranged between CMs of rats and pigs. The repolarization fraction, quantified as (APD_{90} – APD_{30})/ APD_{90}, was significantly higher in human CMs, compared to the other species.

The cell surface area of CMs isolated from human, porcine and equine atrial tissue was larger than in rats and mice, and there was a linear correlation between surface area and the APD_{90}.

On a transcriptomic level, we found unique ion channel expression profiles and identified the most relevant channels for each species expression-wise. Ryanodine receptors, voltage dependent anion channels and chloride intracellular channels belonged to the top expressed channel groups in all datasets. Regarding voltage-gated sodium channels, in human right atrial tissue *SCN1B* was more abundant than *SCN5A*, while *SCN5A* was the most prominent sodium channel in porcine atria. Regarding voltage-gated potassium channels, among other things, *KCNA5*, *KCNH2* and *KCNC4* were enriched in human atria, compared to other species.

Conclusion:

We identified similarities and differences in electrophysiological properties between human atria and different animal species, which will help to assess results from animal studies and to investigate and translate new therapeutic strategies for atrial rhythm disorders.