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Response by Li et al to Letter Regarding Article, "Adenosine-induced atrial fibrillation: Localized reentrant drivers in lateral right atria due to heterogeneous expression of adenosine A1 receptors and GIRK4 subunits in the human heart"

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In Response

We thank Dr. He for his comments on our study[1] and for the interesting points he raises. In our functional and molecular mapping study[1] of human hearts *ex vivo*, we demonstrated that adenosine provokes atrial fibrillation (AF) with a higher activation frequency in the right atria (RA) versus the left atria (LA) due to localized reentrant drivers in lateral RA. Furthermore, our study revealed a high RA-to-LA protein expression gradient of adenosine A1 receptor and GIRK4, a subunit of its downstream channels ($I_{K,Ado}$) in the human heart. This gradient led to significantly greater RA vs. LA repolarization sensitivity in response to adenosine. Selective atrial GIRK channel blockade counteracted adenosine-induced APD shortening and prevented AF induction.

The previous study[2], which Dr. He referred to, had found that higher plasma level of adenosine deaminase (ADA) may be associated with low occurrence of paroxysmal AF. The higher ADA concentrations could accelerate the degradation of adenosine, which therefore exerted the protective effects on the onset of paroxysms of AF. This important study supports the hypothesis[4] that higher levels of endogenous adenosine may lead to AF in patients, and the adenosine signaling pathway may prove to be a valuable target for pharmacological treatment of AF.

When pursuing this avenue of treatment, it is important to consider that adenosine is a key regulator within the cardiovascular system and throughout the body. Adenosine elicits various essential biological responses from the modulation of coronary flow, heart rate, and contraction, to cardioprotective effects during ischemia[3]. Although the reduction of endogenous adenosine levels by modulating its metabolism[2] or blocking A1 receptors[4] could potentially prevent AF, these methods would diminish the cardiac protective effects of adenosine and cause off target effects. We propose that targeting the atrial cardiomyocyte

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Disclosures:
None

specific effectors (such as GIRK4 channels) in the adenosine A1 signaling pathway would provide an efficient treatment for human AF during conditions with increased endogenous adenosine.

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