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# Receptor for advanced glycation end products (RAGE) in atrial fibrillation ☆

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Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and the affected patients have increased risk of a number of complications majorly heart failure and thromboembolism [1]. A number of risk factors have been acknowledged for the development of AF; however, the pathogenesis still remains enigmatic and proposed to be multifactorial. The different factors probably contribute in a different way depending on the main underlying cause of the disease, e.g. hypertension, valvular disease, recent cardiac surgery or others involving inflammatory processes to varying degrees [1–3].

There is an interesting converging data from the animal studies, epidemiological studies and intervention trials, which demonstrates a pivotal role of the inflammation in the pathophysiology of AF [2,4]. Besides this there is evidence that the inflammatory process at least in part is a result of the arrhythmia [5]. Of note, true inflammation (e.g. invasion of inflammatory cells) is reported to be rarely seen in fibrillating atria [3,6]. AF has been demonstrated to cause significant changes in the electrophysiology and atrial architecture and therefore, considered to be a conformational disorder instead [3,6]. Despite all these studies, whether this inflammatory milieu is a cause or consequence of the rhythm disorder is still a matter of debate and a number of questions still remain to be unveiled.

RAGE (receptor for advanced glycation end products) signaling has been extensively described as a malefactor in various pathophysiological conditions. We have recently reviewed the role of multi-ligand receptor i.e. RAGE in context to various vascular diseases, which have a pathophysiologically important inflammatory component in normoglycemic conditions such as atherosclerosis, hypertension, and Takayasu's arteritis [7]. We appreciate the supportive comments by Zhang et al. [8] in response to our recent review article [7]. Recent evidences which are majorly derived from diabetic experimental animals and diabetic subjects conceptually support potential role of inflammation in the pathophysiology of AF, and Zhang et al. have provided insight and extended the current knowledge of RAGE biology in AF and its importance as biomarker and therapeutic target in atrial fibrillation [8].

Also, there are few other diseases, which have pathophysiology of underlying inflammation and need to be explored in the near future to determine the importance of RAGE signaling. For instance, inflammation is an important component in neurodegenerative diseases where RAGE and its ligands are suggested to play important roles [9]. Also, chronic inflammation is known to predispose to cancer, and tumor development is suggested to become enhanced due to inflammation induced by RAGE signaling [10]. RAGE-ligand signaling has also been implicated in T-cell mediated adaptive immune response in various autoimmune diseases [11].

In conclusion, RAGE and its various ligands have now well established roles in various vascular and inflammatory pathologies described here and elsewhere [7,12]. Other pathologies (e.g. atrial fibrillation, stroke, autoimmune diseases and rheumatologic diseases, and cancer), however, require more preclinical studies to define the role of RAGE signaling. Cumulative approach of biochemical and cell biological studies of cell and tissue culture and human and animal pathological tissues will be of importance to understand and to extend the present knowledge RAGE-ligand biology.

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# Mapping and ablation of focal arrhythmia: Should we use three-dimensional mapping systems?

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Focal arrhythmia can be conventionally ablated using multiple electrophysiology catheters including duodecapolar catheters after evaluating preprocedural arrhythmic ECG. The precise localization of the arrhythmia focus can be delineated by mapping maneuvers such as activation sequence compared to the reference catheter or surface ECG. Fluoroscopic anatomy should be well known for conventional purposes. However, recently 3-dimensional mapping tools and methods have been exponentially and widely used due to prolonged procedural and fluoroscopy times and relatively lower successful ablation rates during conventional technique. We performed a successful radio frequency ablation of idiopathic ventricular arrhythmia originating from the anterolateral free wall of the tricuspid annulus using 3-dimensional electroanatomic mapping system [1]. Liu et al. demonstrated a successful ablation of the atrial tachycardia originating from the similar region using another 3-dimensional mapping system, a noncontact mapping system [2]. As with the electroanatomic mapping system, the noncontact system has similar inherent characteristics of a global view of local activation and propagation, catheter manipulation without fluoroscopy, marking points during both mapping and ablation, and annotation of relevant structures on the virtual geometric maps. The most important advantage of the noncontact mapping system is mapping of transient or non-sustained and hemodynamically unstable arrhythmia because the system has multiple unipolar electrodes allowing simultaneous recording of more than 3000 signals. Another important advantage of this system is no need for specific ablation catheters because it is compatible with any ablation catheter. Besides these advantages, the noncontact mapping system has some inherent disadvantages including no simultaneous multiple cardiac chamber rendering difficulty in positioning of the balloon in enlarged cardiac chambers and signal attenuation or loss for distances greater than 4 cm from the multielectrode array.

In conclusion, non-fluoroscopic computer-based 3-dimensional mapping systems including the electroanatomic and noncontact mapping should be kept in mind and furthermore should be used precisely to map and successfully ablate the arrhythmia, especially the focal arrhythmia.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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