Seeking a Better Experimental Model of Atrial Fibrillation

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Rhythm control therapy for paroxysmal atrial fibrillation (AF) has extensively advanced in the past couple of decades by catheter ablation (CA) for pulmonary vein isolation.¹ However, the success rate of CA for persistent AF is still limited, even with an additional ablation strategy.² The obstacle to the treatment of persistent AF is the accumulation of AF substrate in the atria. The AF substrate has electrical aspects due to changes in ion channel expression and function, and structural aspects based on inflammation, fibrosis, and apoptosis in atrial tissue. To improve therapeutic strategies for persistent AF, it is necessary to clarify the relationship between the AF substrate and arrhythmogenicity. As an example, rotor activity is considered one of the critical mechanisms for the maintenance of AF;³ however, the contribution of the AF substrate to generate the rotor remains unclear. Therefore, a more detailed understanding of the characterization of the AF substrate is needed using experimental models.

In this issue of the Journal, Horii et al reported that laser irradiation on the atrial surface could create a substrate of atrial arrhythmia using murine perfused heart.⁴ The authors developed a retrograde perfusion method that avoids mechanical damage to the atria, and established a laser irradiation system that controls the shape of the injured area. They found that the circular-shaped lesion was unable to induce atrial arrhythmogenicity; however, the wedge-shaped lesion successfully induced long, persistent atrial tachycardia in a

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murine heart, although fine AF could not be induced. They also showed that the irradiated area had a reduced content of nicotinamide adenine dinucleotide, which contributed to the substrate of atrial tachycardia.

Currently, several experimental subjects are used in cardiac electrophysiological analysis: (1) single cardiomyocyte; (2) cell sheet; (3) cardiac organoids; (4) section of the heart; (5) whole heart; and (6) computational simulation model (**Table**). Single cells include cultured cells, primary cardiomyocytes, cardiomyocytes derived from embryonic stem cells or induced pluripotent stem cells, and are mainly analyzed with the patch clamp technique.^{5,6} These cells are also used for the generation of a cell sheet for the analysis of intercellular conduction and propagation. The cell sheet has a 2-dimensional structure and is assessed with optical mapping or multi-electrode array.⁷ Cell-to-cell conduction can also be assessed using a dual whole-cell patch clamp with coupled cells. The generation of cardiac organoids is recently established, and several studies reported that it showed atrial and ventricular electrophysiological properties.^{8,9} In contrast to a cell sheet, the cardiac organoid has the potential to be analyzed in a 3-dimensional model and is useful for the investigation of arrhythmias.

To analyze the electrical behavior and mechanism of

Table. Subjects of Cardiac Arrhythmia Research

Subject	Arrhythmia induction	Assessment method	Note
Cell	Impossible	Patch clamp Optical mapping	It enables the clarification of the function of the ion channel. The dual whole cell patch clamp can assess cell-to-cell conduction.
Cell sheet	Possible	Multi-electrode array Optical mapping	Most of the experimental system is produced to assess a 2-dimensional model.
Organoid	Possible	Optical mapping	This is a promising experimental subject for 3-dimensional analysis, but it still needs to be well-established.
Section of the heart	Possible	Electrocardiogram Local electrogram Optical mapping	Isolated atrial tissue can be used to assess the electrophysiological properties of the atrium.
Whole heart	Possible	Electrocardiogram Local electrogram Optical mapping	Generally, it is difficult to induce arrhythmias in the small animal heart.

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received August 31, 2021; accepted August 31, 2021; J-STAGE Advance Publication released online October 9, 2021

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ISSN-1346-9843

cardiac arrhythmias, especially complex arrhythmias such as AF, the best way is to use the actual heart. Various mammalian hearts, including the human heart, which is obtained during heart transplantation, large animal hearts (horses, goats, pigs, dogs, etc.), and small animal hearts (rabbits and rodents) have been used for the basic research of arrhythmias. In large animals, chronic rapid atrial pacing is commonly performed for the induction of AF.¹⁰ Moreover, it is possible to observe spontaneous AF in some healthy large animals.¹¹ The large animal heart can be evaluated with the same electrophysiological study equipment used clinically.

Because of its ease of accessibility, handling, and genetic modification, the murine heart has been studied for cardiac arrhythmias. However, the mouse heart has difficulty in the inducibility of arrhythmias, especially atrial arrhythmias including AF, due to its small size. Several studies reported the inducibility of sustained atrial tachyarrhythmia in the transverse aortic constriction model,¹² and spontaneous AF in genetically modified mouse strains.^{13,14} A high-resolution optical mapping enables a detailed assessment of propagation. However, there is no established method with a high success rate in inducing sustained atrial arrhythmia in wild-type murine hearts. In this regard, the report by Horii et al.⁴ provides a novel approach to induce atrial arrhythmia in the murine heart by artificial generation of the AF substrate by laser irradiation. This is a major step forward in the basic research on AF, and future developments are highly anticipated.

Disclosures

The authors have no conflicts of interest to declare.

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