LETTER TO THE EDITOR

Difficulties in the use of cost-effective mouse models of atrial fibrillation

Dificultades en el uso de modelos murinos costo-efectivos para fibrilación auricular

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To the editor,

In the past 10 years, the number of studies claiming to induce atrial fibrillation (AF) in mice has increased. These studies include a substrate, such as structural heart disease, pressure overload, obesity, diabetes mellitus, inflammation, ethanol exposure, or the use of selective targets identified through genome-wide association studies, as well as genetic mutations in ion channels[1].

The mouse atrial surface area is < 35 mm^2, and this limited size makes it difficult to sustain atrial tachyarrhythmias. In fact, the most effective models for AF typically involve large animals. Some research groups report that it is possible to sustain a micro-reentrant circuit in mouse models, even though the atrial tissue does not meet the critical mass requirement of > 100-200 mm^2 to induce AF[2]. Garrey postulated in 1914 that "Any small auricular piece will cease fibrillating[3]". In studies reporting positive AF induction in mouse models, carbachol and electrical stimulation are often included as cost-effective methods for inducing AF, despite the limitation that such arrhythmias are non-spontaneous.

As a cost-effective alternative, and based on the positive results reported by Chiba and Hashimoto (1971) in beagle dogs using carbachol and epinephrine, induction of AF through pharmacological protocols appears feasible. In a pilot study, we utilized nine wild-type mice divided into three groups. Administration of carbachol combined with epinephrine at higher doses in one group resulted in sinus pause, sinus bradycardia, and severe bradycardia when delivered by epicardial drip (thoracotomy and mechanical ventilation were used). First-degree atrioventricular block was observed in one out of three mice, but no mouse developed AF. Fig. 1 shows representative electrocardiograms illustrating each observed effect.

Carbachol is a potent compound with a longer duration of action compared to acetylcholine. In the study performed by Chiba and Hashimoto, carbachol alone was sometimes insufficient to trigger AF; therefore, epinephrine was administered to enhance the adrenergic response. Cholinergic stimulation shortens the action potential, and carbachol, as a muscarinic receptor agonist, is reported to reduce atrial refractoriness and facilitate reentrant circuits. Furthermore, it has been proposed that epinephrine can help trigger AF by increasing adrenergic activity[4].

In recent decades, research on acute AF in mice has commonly employed protocols that combine carbachol administration with high-frequency electrical stimulation of the atrium to induce AF, potentially altering the activity of intrinsic cardiac ganglia. In 2022, Fu et al. compared various murine AF models, including those using carbachol and burst pacing. Using optical mapping, they observed that the induced atrial

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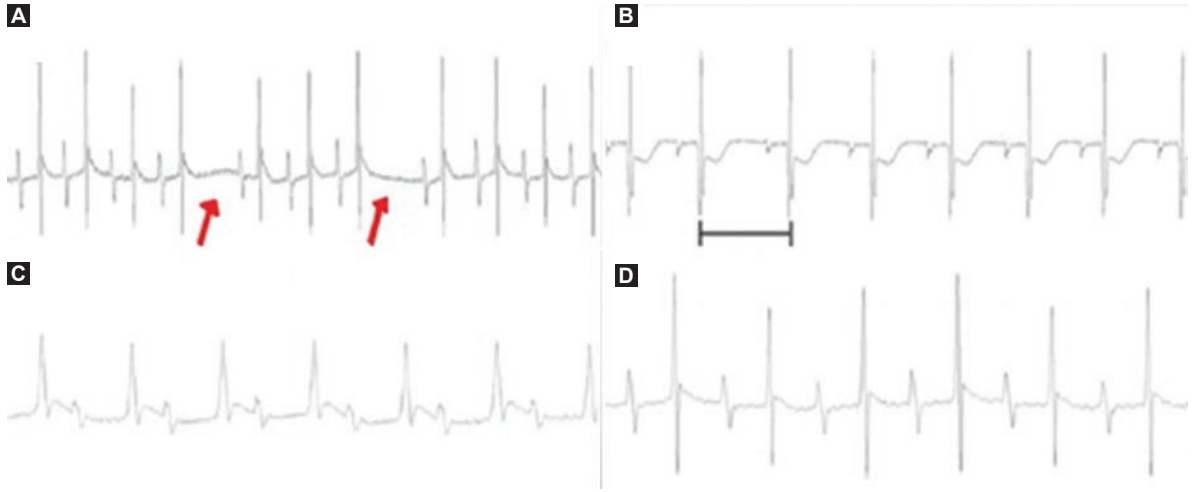

Figure 1. A*: Sinuses pause (red arrows).* **B***: Bradycardia.* **C** *and* **D***: first-degree atrioventricular block.*

tachyarrhythmias more closely resembled atrial flutter-like arrhythmias rather than typical AF[5].

Genetically modified mice, which provide a more physiologically relevant model, have proven to be the most effective for developing spontaneous AF, although they are not the most cost-effective option. The literature suggests that the combination of carbachol and electrical stimulation remains the most cost-effective method to induce AF to date, despite its limitations of producing non-spontaneous arrhythmias and challenges in interpreting positive AF cases[5]. However, this method is not always affordable for researchers in underdeveloped countries. Therefore, exploring alternative pharmacological and instrumental approaches is crucial to advancing arrhythmia research, as well as improving access to modern techniques for verifying AF in mice, such as optical mapping.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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