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Editorial

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Can Artemisinin Be a Game Changer Even as an Antiarrhythmic Drug?

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▸ See the article "Antiarrhythmic Effect of Artemisinin in an Ex-vivo Model of Brugada Syndrome Induced by NS5806" in volume 53 on page 239.

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Since Brugada syndrome (BrS) was first described by the Brugada brothers in 1992, extensive studies have been conducted on this disease's pathophysiology, clinical manifestation, natural course, and risk stratification. Although there have been significant advancements, the management of BrS is still challenging. The implantation of an implantable cardioverter-defibrillator (ICD) is a Class I recommendation for patients who have successfully resuscitated from sudden cardiac arrest due to polymorphic ventricular tachycardia or ventricular fibrillation and Class IIa recommendation for patients with Brugada type I pattern electrocardiogram and arrhythmic syncope.[1] Pharmacologically, quinidine should be considered in patients with BrS who qualify for an ICD but have a contraindication, decline, or recurrent ICD shocks (IIa). Isoproterenol infusion is also a Class IIa recommendation for BrS patients suffering electrical storms. Recently, catheter ablation of BrS was suggested, and elimination of triggering premature ventricular complexes and/or right ventricular outflow tract epicardial substrate is a Class IIa recommendation for BrS patients with recurrent appropriate ICD shocks and refractory to drug therapy.[1-3] However, ICDs cannot prevent the occurrence of life-threatening ventricular arrhythmias and have significant side effects such as infection, lead-related problems, and inappropriate shocks that cannot be easily ignored. In addition, Quinidine has undesirable side effects, and its availability is limited, especially in regions where BrS is endemic.[2] Isoproterenol does not have an orally available form. The catheter ablation gives us the hope that definitive or curative treatment for BrS could be possible. However, the data is still insufficient, and the operator's experiences can primarily affect the procedure results. Hence, the current treatment options for BrS are limited and often ineffective.

Artemisinin was first isolated from Artemisia annua L by Chinese scientist Youyou Tu in 1972. It burst onto the field of antimalarial treatment drugs that were in crisis due to drug-resistant Plasmodium falciparum malaria infection, redefined the landscape of antimalarial therapy, and became a game changer.[4] Artemisinin-based combination therapy led to significant improvements in parasite clearance and rapidly diminished symptoms. Currently, the drug is recommended as the first-line treatment of uncomplicated falciparum malaria infection.[5]

On the other hand, as treatment experience has accumulated, drug repositioning of artemisinin is being actively attempted in various fields, including antiviral, antiparasitic, antifungal, anticancer, anti-immune, and anti-inflammatory activities.[6] In this issue of the

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Korean Circulation Journal, Jeong et al.[7] reported the results of their investigation regarding the anti-arrhythmic effect of artemisinin. They used a canine experimental model of BrS induced by NS5806, an I_{to} channel agonist. The results showed that artemisinin effectively suppressed ventricular tachyarrhythmia and recovered the action potential dome of the right ventricular epicardium in all experimental preparations. The authors speculated that these results were mainly derived from artemisinin's I_{to} channel inhibition effect. The inherent limitations of the study using the canine experimental model, which induces the Brugada electrocardiography manifestation by sodium/calcium channel blocker and I_{to} channel agonist, are also well described that we should keep in mind when accepting the results.

Interestingly, malaria-related drugs also show a relation with arrhythmias. Quinidine is a class IA anti-arrhythmic drug that is still being used in severe malaria infections. Chloroquine and its derivative hydroxychloroquine are the first-line antimalarial drug that also has an inhibitory function on I_{Kr} and resultant mild QT prolongation. Additionally, many experimental studies have revealed that quinidine and chloroquine can directly alter various cell surface ionic currents (I_{Na}, I_{to}, $I_{Ca\text{-}L}$, I_{Kr}, $I_{KATP,}$ and I_{K1}) and disrupt intracellular Ca^{2+} handling and mitochondrial function, causing increased reactive oxygen species generation and tissue fibrosis.[8] Research on artemisinin has been limited, but this study has experimentally confirmed the anti-arrhythmic effects of artemisinin.

Although there will be many obstacles to actual use in BrS patients, the fact that artemisinin has already been safely used worldwide for decades to treat malaria is a hopeful sign for drug repositioning. Furthermore, if artemisinin shows efficacy in common arrhythmias such as atrial fibrillation,[9] it may also become a game changer in the field of anti-arrhythmic drugs.

In conclusion, this study revealed the experimental evidence that artemisinin could be an effective treatment option for BrS. Also, the study offers a new perspective on future research about the pharmacological treatment of the BrS and the anti-arrhythmic effect of artemisinin.

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