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EDITORIAL COMMENT

Inhibition of Triggered Activities in Pulmonary Veins

Do Statins Have a Direct and Clinically Relevant Antiarrhythmic Effect?*

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Statins, also known as HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, are the world's most widely prescribed medications. Approximately 24 million people take statins, with >200 million prescriptions filled in 2009 in the U.S. alone. Rapidly accumulating basic and clinical evidence shows that the beneficial effects of statins on cardiovascular system extend well beyond their primary lipid-lowering effect in primary and secondary prevention of coronary heart disease. Among the pleiotropic effects of statins, the most intriguing is their beneficial effect in prevention of atrial fibrillation (AF). In the GISSI-HF (Effect of Rosuvastatin in Patients with Chronic Heart Failure) trial in which patients were randomly assigned to treatment of rosuvastatin at 10 mg daily or placebo, rosuvastatin reduced the incidence of new onset of AF in patients with stable heart failure after a median follow-up period of 3.7 years (1). The clinical data indicate that the reduced risk of AF after use of statins for a number of years appears to be independent of the reduction in serum cholesterol levels (2). Conversely, statins also reduce the risk of AF in the setting of acute events, such as after cardiac surgery or noncardiac thoracic surgery, in which AF occurs within a relatively short and fixed time window (often in days) (3).

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The question is how statins affect electrophysiological properties of the atria and adjacent tissues such as pulmonary veins that participate in the development of AF. The pleiotropic properties of statins, which may be beneficial to health of the atria and pulmonary veins so that the substrate and the risk factors for the development of AF can be limited, include their anti-inflammatory effect (4), inhibition of platelet activation (5), improvement of endothelial function (6), preventative and reverse atrial remodeling (7), and reduction of oxidative stress. However, these effects on the electrical properties of the atria and pulmonary veins are indirect and undistinguished.

In this issue of the *Journal*, Sicouri et al. (8) reported their interesting findings that simvastatin, one of the commonly prescribed statins, exerts a direct antiarrhythmic effect in the pulmonary veins by suppressing triggered activities responsible for the development of AF (8). They found that simvastatin at concentrations of 10 to 20 nM suppressed or abolished late-phase 3 early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs), which were elicited by acetylcholine, isoproterenol, high extracellular Ca^{2+}, or their combination, plus rapid pacing, in the endocardial extension of atrial muscle covering the pulmonary veins. It is well known that EAD- and DAD-dependent triggered activities are responsible for a variety of cardiac arrhythmias (9). Recent clinical evidence and basic research studies have shown that triggered activities from the pulmonary veins contribute importantly to the development of AF (10,11). In the study by Sicouri et al. (8), it is particularly interesting that simvastatin can abolish the late-phase 3 EADs induced by acetylcholine plus high extracellular Ca^{2+}. Unlikely EADs observed in the ventricular tissues under condition of delayed repolarization, the late-phase 3 EADs occur in the atria or pulmonary veins when action potential duration becomes markedly shortened (9,12). The late-phase 3 EAD is thought to be an important source for atrial extrasystoles capable of initiating AF. This is because the condition favoring the genesis of the late-phase 3 EADs also shortens the atrial impulse wavelength, facilitating the formation of a re-entrant substrate.

The study by Sicouri et al. (8) has significant clinical implications. First of all, statins such as simvastatin are the most commonly prescribed medications for primary and secondary prevention of coronary heart disease, whereas AF is the most common cardiac arrhythmia that requires medical attention. In other words, a large population of people who require the therapy of statins are likely to have a higher risk for the development of AF. Secondly, if statins exhibit a direct and clinically relevant antiarrhythmic effect, statins would have more broad clinical applications. In the events in which AF often occurs within a few of days, such as at a perioperative stage or shortly after electrical cardioversion of AF, direct antiarrhythmic effects of statins would provide prompt protection in reducing the AF incidence. This appears supported by clinical evidence (3,13).

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The underlying ionic mechanisms for the effects of simvastatin on electrical activities of the pulmonary veins are unknown. In addition to their suppression of EADs and DADs, simvastatin also caused a significant decrease in action potential amplitude and marked use-dependent depression of maximum rate of rise of action potential upstroke (Vmax) (8). These effects of statins are similar to those of ranolazine, a compound that inhibits fast and late sodium currents. Therefore, one would attribute the effects of simvastatin to the inhibition of the sodium current. Surprisingly, the data from the study by Sicouri et al. (8) showed that simvastatin up to 5 μM did not produce any significant effects on the fast as well as the late sodium current. The authors explained it and pointed out that the effects of simvastatin on Vmax and action potential amplitude were secondary to simvastatin-induced depolarization and a more positive take-off potential at the faster rates (8). However, that cannot clearly explain why simvastatin inhibits both EADs and DADs, because depolarizations to a more positive resting membrane potential per se have no direct inhibitory influence on EADs and DADs. Further studies to explore ionic mechanisms of statins are necessary.

As simvastatin is highly bound to the plasma protein, its normal unbound concentration in plasma is in the range of 0.5 to 1 nM (14). That appears to be lower than the concentrations (10 to 20 nM) used in the Sicouri et al. (8) study. One may question whether simvastatin could accumulate in atrial myocytes or pulmonary veins to a concentration range in which clinically relevant electrophysiological effects can be observed. However, it should be emphasized that the real human plasma concentration of simvastatin can fluctuate in a relatively large range and be significantly different in individual patients. In addition, numerous medications with a property to inhibit CYP450 isoenzymes can significantly increase the plasma concentration of statins. Some of them can result in a >20-fold increase in bioavailability of statins (15). More importantly, several commonly used drugs in treatment of AF, including amiodarone, verapamil, and digoxin, also increase the plasma concentration of statins (15). That probably explains why the combination of amiodarone and statins improves freedom from recurrence of AF after successful cardioversion (13). In future studies, statins should be evaluated in a more broad range of concentrations for their direct antiarrhythmic effects in vitro as well as in vivo models.

Although there is clinical evidence that use of statins is also associated with less risk of ventricular arrhythmias (16), direct antiarrhythmic effect of statins in the ventricles has not been reported. Direct inhibition of EADS and DADs by statins in the pulmonary veins indicates that statins may potentially exert a similar protective effect in the ventricles, and a role of statins through their antiarrhythmic effects in reduction of all-cause mortality cannot be ruled out. It would be, therefore, interesting to test whether statins have any antiarrhythmic effects in the ventricles.

As discussed, the finding that statins exert direct antiarrhythmic effects in an animal model is encouraging and calls for further basic and clinical research in this field. The future studies on statins should focus on their ionic mechanisms, dose-response relation, safety in terms of proarrhythmic potentials, and clinical outcomes in patients prone to arrhythmias of cardiac arrhythmias. Only after these investigations will we be more confident in applying statins to our patients for the purpose of antiarrhythmia therapy.

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