Influences of rapid pacing-induced electrical remodeling on pharmacological manipulation of the atrial refractoriness in rabbits

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ABSTRACT

Electrical remodeling plays a pivotal role in maintaining the reentry during atrial fibrillation. In this study, we assessed influence of electrical remodeling on pharmacological manipulation of the atrial refractoriness in rabbits. We used an atrial electrical remodeling model of the rabbit, subjected to rapid atrial pacing (RAP; 600 beats/min) for 2–4 weeks, leading to shortening of atrial effective refractory period (AERP). Intravenous administration of dl-sotalol (6 mg/kg), bepridil (1 mg/kg), amiodarone (10 mg/kg) or vernakalant (3 mg/kg) significantly prolonged the AERP both in the control and RAP rabbits. The extents in the RAP rabbits were similar to those in the control animals. On the other hand, prolonging effects of intravenously administered ranolazine (10 mg/kg) or tertiapin-Q (0.03 mg/kg) on the AERP in the RAP rabbits were more potent than those in the control animals. These results suggest that rapid pacing-induced electrical remodeling effectively modified the prolonging effects of ranolazine and tertiapin-Q on the AERP in contrast to those of clinically available antiarrhythmic drugs, dl-sotalol, bepridil amiodarone and vernakalant.

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1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia found in clinical practice, which is closely related to an increased long-term risk of stroke, heart failure, and all-cause mortality (1,2). Class I or III antiarrhythmic drugs are primarily used for patients with AF to suppress reentry in the atria via a prolonging action of effective refractory period. However, the antiarrhythmic drugs sometimes have limitations due to adverse effects such as a decrease of ventricular conduction or contraction at therapeutic dose ranges, leading to the modest efficacy for AF (3–5).

The pathophysiology of AF has been a subject of active investigation for more than a century, and the mechanisms of AF are recognized as being multifactorial and sharing properties of reentry, automaticity, and triggered activity (3–5). Furthermore, AF itself leads to various remodelings in the atria, such as the shortening of the action potential duration and atrial effective refractory period (AERP), an increase in heterogeneity of refractoriness, changes in ion channel expression and conductivity, and development of fibrosis (3–5). Inconveniently, such progressive electro-anatomic remodelings of the atria facilitates perpetuation of AF, which is often refractory to conventional drug therapy. Sicilian Gambit classification is a newer approach to select proper antiarrhythmic drugs for an individual patient based on its multiple actions on arrhythmogenic mechanisms (6). Because of the complex pathophysiology of AF, further pharmacological information is needed to prescribe proper drugs for patients with persistent AF.

To clarify influence of electrical remodeling on pharmacological manipulation of the atrial refractoriness, in this study, we compared effects of several antiarrhythmic drugs on the normal and electrically remodeled atria in rabbits, since electrical remodeling plays a pivotal role in maintaining the reentry during AF (3–5). We assessed following 6 drugs; dl-sotalol (a blocker of Ik,C and β-adrenoceptor), bepridil (a multi-ion channel blocker), amiodarone (a blocker of multi-ion channels and adrenoceptor), vernakalant (a multi-ion channel blocker), ranolazine (a late Ih blocker), and tertiapin-Q (an I(ACh) blocker). We used an atrial electrical remodeling model of the rabbit, which was subjected to rapid atrial pacing (600 beats/min) for 2–4 weeks, leading to shortening of AERP. To avoid heart failure-related atrial remodeling, experiments were performed using the heart with complete development of fibrosis (3–5).
atrioventricular block under the constant ventricular pacing (180 beats/min).

2. Materials and methods

All animal experiments were reviewed and approved by the Experimental Animal Committee of the R&D Department of TOA EIYO Ltd, Fukushima Research Laboratories (Fukushima, Japan).

2.1. Rabbit model of rapid atrial pacing

Male New Zealand White rabbits (Japan SLC, Inc., Shizuoka, Japan) weighing 3.0–3.5 kg were used for this study. The rabbits were initially anesthetized with ketamine hydrochloride (35 mg/kg, i.m.) and xylazine (5 mg/kg, i.m.), and the anesthesia was maintained by a continuous intravenous infusion of ketamine hydrochloride (20 mg/kg/h) and xylazine (3 mg/kg/h). After intubation with a tracheal cannula, left thoracotomy was performed under mechanical ventilation. Two pairs of recording/pacing electrodes (Physiotech, Tokyo, Japan) were sutured to the left atrial appendage (LAA) and left ventricle. The electrode leads were tunneled subcutaneously to the back for recording cardiac electrical activity and electrically pacing with an external pacemaker (PACE 101H, OSYPKA Medical, Berlin, Germany). The complete atrioventricular block was induced using the catheter ablation technique, as previously described (7), and the ventricle was electrically driven at a pacing rate of 180 beats/min throughout the experiment. The rabbits were divided into two groups as follows: control rabbits and rabbits subjected to rapid atrial pacing (RAP). One week later, the left atrium was electrically paced at 600 beats/min using an external pacemaker (PACE 101H, OSYPKA Medical) with an output of twice-threshold voltage (n = 24). On the other hand, the rapid atrial pacing was not delivered in a group of control rabbits (n = 32).

2.2. Hemodynamics and electrophysiological measurements

More than 2 weeks after the start of rapid atrial pacing, the rabbit was anesthetized with ketamine hydrochloride (17 mg/kg, i.m.) and xylazine (2.5 mg/kg, i.m.), and the anesthesia was maintained by a continuous intravenous infusion of ketamine hydrochloride (20 mg/kg/h) and xylazine (3 mg/kg/h). The surface lead II electrocardiogram (ECG) was obtained from the limb electrodes. An indwelling needle was placed in the central auricular artery for monitoring of the blood pressure. After the rapid atrial pacing was temporarily stopped, the blood pressure, surface ECG, and atrial electrogram were monitored with a multi-channel amplifier (MEG-6108, Nihon Kohden, Tokyo, Japan). Each measurement of ECG or atrial electrogram was the mean of 10 consecutive recordings.

The AERP was measured at basic cycle lengths of 250, 200 and 150 ms with a train of 8 basic stimuli (S1) followed by a premature extrastimulus (S2) at 2-ms decrements using a programmable stimulator (SEC-4103, Nihon Kohden, Tokyo, Japan) with twice-threshold voltage at a 1-ms pulse duration. The AERP was defined as the shortest S1–S2 interval that captured the atria, as shown in Fig. 1A. At each evaluation of the electrophysiological parameters, the atrial diastolic threshold was measured by delivering 250 ms cycle length pacing with a pulse width of 1 ms.

For induction of AF, the LAA was paced at 900 beats/min for 5 s with 4 times of the diastolic threshold voltage using an electrical stimulator (SEC-4103, Nihon Kohden, Tokyo, Japan). AF was defined

Fig. 1. Typical LAA electrograms and surface ECG in the control and rapid atrial pacing (RAP) rabbits. (A) Representative LAA electrograms for measurement of AERP in control and RAP rabbits. (B) Representative electrograms of AF induced by burst pacing in control and RAP rabbits. A: atrial electrogram, V: ventricular electrogram. The arrows indicate the reactive atrial excitation. ECG: electrocardiogram, LAA: left atrial appendage.
as a rapid irregular atrial rhythm lasting >1 s, resulting in an irregular baseline of the ECG. The burst pacing was repeated 10 times, and the AF duration was calculated by averaging the sustained period of AF after the burst pacing. When the atrial fibrillation was sustained for >60 s, it was terminated electrically.

2.3. Experimental protocol

When analyzing effects of each drug on the atrium, the rapid atrial pacing was stopped during the assessment. During the stabilization period of 30 min, the AERP was measured to check an extent of electrical remodeling of the atria. After baseline cardiovascular and electrophysiological variables were obtained, a drug was administered intravenously via the marginal ear vein over 10 min, and each variable was assessed 10 min after the start of the drug infusion. The dose of each drug except for ranolazine was chosen based on our preliminary study using normal rabbits, where the AERP was prolonged by 10 mg/kg did not prolonged the AERP up to the criterion in normal rabbits, 10 mg/kg of ranolazine was chosen for this study, because higher doses of ranolazine showed severe hypotension. After the termination of the electrophysiological assessments, the rapid atrial pacing was resumed.

The pharmacological evaluation with dl-sotalol, bepridil, amiodarone, vernakalant, ranolazine or tertiapin-Q was performed 2–4 weeks after the start of RAP. Seven out of 24 rabbits receiving the RAP were additionally used for pharmacological evaluation after a washout period of more than 2 days. Since the elimination half-life of amiodarone is known to be long (47 days), no drug was evaluated after the assessment of amiodarone.

2.4. Drugs

dl-Sotalol, bepridil hydrochloride and ranolazine dihydrochloride were purchased from Sigma Aldrich (St. Louis, MO, USA). Amiodarone hydrochloride (Ancaron Inj™) was purchased from Sanofi Co., Ltd. (Tokyo, Japan). Vernakalant hydrochloride was purchased from Haoyuan Chemexpress Co., Ltd. (Shanghai, China). Tertiapin-Q was purchased from PEPTIDE institute Inc (Osaka, Japan). Ketamine hydrochloride (Ketalar™) was purchased from Daichi-Sankyo (Tokyo, Japan). Xylazine (Selact™) was purchased from Bayer Health Care (Tokyo, Japan). dl-Sotalol, vernakalant and tertiapin-Q were dissolved in saline. Amiodarone was diluted with 5% glucose. Bepridil was dissolved in saline containing 10% DMSO and 5% Tween 80.

2.5. Statistical analysis

Data are presented as the mean ± S.E.M. The statistical significances of differences in paired data were evaluated by the paired t-test, whereas those in unpaired data were evaluated by Student’s t test or Aspin-Welch t test. The statistical significances of multiple differences were evaluated by Tukey test. All data analyses were performed using EXSSUS version 7.7.1 (CAC EXICARE, Osaka, Japan). P-value of <0.05 was considered as statistically significant.

3. Results

3.1. Electrophysiological characteristics of the RAP rabbits

The results of cardiovascular and electrophysiological variables are summarized in Table 1. There was no significant difference in the mean blood pressure, atrial rate, P-wave duration or QT interval between the two groups. The AERP in the RAP rabbits was significantly shorter than that in the control rabbits in each pacing cycle length of 250, 200 or 150 ms. As shown in the Fig. 1B, AF was effectively induced by burst pacing to the LAA in the RAP rabbits. AF inducibility and duration in the RAP rabbits were significantly greater than those in the control rabbits.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>RAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>76 ± 1</td>
<td>77 ± 1</td>
</tr>
<tr>
<td>Atrial rate (bpm)</td>
<td>207 ± 7</td>
<td>190 ± 7</td>
</tr>
<tr>
<td>P-wave duration (ms)</td>
<td>38 ± 1</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>172 ± 2</td>
<td>175 ± 3</td>
</tr>
<tr>
<td>AERP CL – 250 (ms)</td>
<td>76 ± 1</td>
<td>56 ± 1***</td>
</tr>
<tr>
<td>AERP CL – 200 (ms)</td>
<td>77 ± 1</td>
<td>58 ± 1***</td>
</tr>
<tr>
<td>AERP CL – 150 (ms)</td>
<td>77 ± 1</td>
<td>60 ± 1***</td>
</tr>
<tr>
<td>AF inducibility (%)</td>
<td>≥ 32</td>
<td>57 ± 5***</td>
</tr>
<tr>
<td>AF duration (s)</td>
<td>0.1 ± 0.0</td>
<td>3.4 ± 0.9**</td>
</tr>
</tbody>
</table>

Data are represented as mean ± S.E.M. from the control rabbits (n = 32) and rapid atrial pacing (RAP) rabbits (n = 24) more than 2 weeks after the start of rapid atrial pacing. Data are represented as mean ± S.E.M. from the control rabbits (n = 32) and rapid atrial pacing (RAP) rabbits (n = 24) more than 2 weeks after the start of rapid atrial pacing.

3.2. Effects of 6 antiarrhythmic drugs on the AERP in the control and RAP rabbits

After the cessation of rapid atrial pacing, we confirmed that the AERP was unchanged during the experimental period in the RAP rabbits (n = 6, data not shown). Figs. 2 and 3 summarize the effects of intravenous administration of dl-sotalol (6 mg/kg, n = 5 for each group), bepridil (1 mg/kg, n = 5 for each group), amiodarone (10 mg/kg, n = 5 for each group), vernakalant (3 mg/kg, n = 5 for each group), ranolazine (10 mg/kg, n = 6 for each group) or tertiapin-Q (0.03 mg/kg, n = 5 for each group) on the AERP in the control and RAP rabbits. dl-Sotalol, bepridil, amiodarone, and vernakalant significantly prolonged the AERPs at each pacing cycle length in the control rabbits, and their extents were similar to those in the RAP rabbits. Tertiapin-Q significantly prolonged the AERP at each pacing cycle length both in the control and RAP rabbits. On the other hand, ranolazine significantly prolonged the AERP only at a pacing cycle length of 150 ms in the control rabbits, whereas the drug significantly prolonged the AERPs at all pacing cycle lengths in the RAP rabbits. The extents of prolonging effect of ranolazine and tertiapin-Q on the AERP in the RAP rabbits were greater than those in the control animals.

3.3. Effects of 6 antiarrhythmic drugs on the burst pacing-induced AF in the RAP rabbits

Effects of the 6 antiarrhythmic drugs on the AF inducibility and AF duration are summarized in Table 2. There was no significant difference in baseline values among the drug treatment groups. The drugs except for amiodarone significantly reduced AF inducibility, and amiodarone potentially decreased it (p = 0.0817). The AF duration was reduced after the administration of the antiarrhythmic drugs, which did not achieve conventional level of statistical significance.

3.4. Effect of 6 antiarrhythmic drugs on the hemodynamics and ECG parameters

The effects of 6 antiarrhythmic drugs on hemodynamics and ECG parameters are summarized in Table 3. The mean blood pressure was decreased by bepridil, amiodarone, vernakalant and...
ranolazine in the control rabbits as well as RAP rabbits. The atrial rate was significantly increased by tertiapin-Q in the control rabbits as well as RAP rabbits. The P-wave duration was significantly prolonged by bepridil, amiodarone and vernakalant in control rabbits, whereas it was increased by vernakalant in the RAP rabbits. The QT interval was prolonged by dl-sotalol, bepridil, amiodarone, vernakalant and ranolazine both in the control and RAP rabbits.

Fig. 2. Effects of dl-sotalol, bepridil and amiodarone on the atrial effective refractory period (AERP) in the control and rapid atrial pacing (RAP) rabbits. dl-Sotalol (left panels, 6 mg/kg, n = 5 for each group), bepridil (middle panels, 1 mg/kg, n = 5 for each group) or amiodarone (right panels, 10 mg/kg, n = 5 for each group) was intravenously administered to the control or RAP rabbits. AERP was measured before and 10 min after the administration of each drug, which are shown in the lower panels. Upper panels show the extents of AERP-prolonging effects. Each data represents the means ± S.E.M. **P < 0.01; ***P < 0.001, compared with corresponding baseline value (Baseline).

Fig. 3. Effects of vernakalant, ranolazine and tertiapin-Q on the atrial effective refractory period (AERP) in the control and rapid atrial pacing (RAP) rabbits. Vernakalant (left panels, 3 mg/kg, n = 5 for each group), ranolazine (middle panels; 10 mg/kg, n = 6 for each group) or tertiapin-Q (right panels; 0.03 mg/kg, n = 5 for each group) was intravenously administered to the control or RAP rabbits. AERP was measured before and 10 min after the administration of each drug, which are shown in the lower panels. Upper panels show the extents of AERP-prolonging effects. Each data represents the means ± S.E.M. *P < 0.05; **P < 0.01; ***P < 0.001, compared with corresponding baseline value (Baseline). †P < 0.05; ‡P < 0.01; §§P < 0.001, compared with corresponding control value (Control).
Data are represented as mean ± S.E.M. *P < 0.05; **P < 0.01, compared with corresponding baseline value.

4. Discussion

In this study, we compared electrophysiological effects of 6 antiarrhythmic drugs on the normal and electrically remodeled atria in rabbits. The extents of prolonging effects of dl-sotalol, bepridil, amiodarone or vernakalant on the AERP in the RAP rabbits were similar to those in the control animals. On the other hand, the AERP-prolonging effects of ranolazine or tertiapin-Q in the RAP rabbits were more potent than those in the control animals.

4.1. Characteristics of rapid atrial pacing model in rabbits

Longer durations of AF or RAP have been shown to induce shortening of the AERP, which is related to the lower success rates of various antifibrillatory treatments when the arrhythmia has lasted for a longer period (3–5). As summarized in Table 1, the AERP was shorter in rabbits receiving RAP for 2–4 weeks than in control animals, which may be associated with greater inducibility and duration of AF in this animal model. Since the P-wave duration was not different between the two animal groups, neither atrial enlargement nor disturbance of intra-atrial conduction associated with congestive heart failure might be induced in the RAP rabbits, whose ventricular rate was maintained at 180 beats/min after the creation of complete atrioventricular block. The mechanisms of AERP shortening after RAP have been proposed using animal models, in which a pronounced reduction of the action potential duration in the atria are associated with reduced I_{CaL} and I_{Ks} caused by the downregulation of the underlying Cav1.2 and Kv4.3 subunit expression as well as an increase in constitutively active I_{KCh}, whereas I_{Kd}, rapid delayed-rectifier K+ current, I_{Kf}, I_{Kur} or I_{CaT} was unaltered (3–5,9–11). We speculate that such mechanisms may be essentially involved in the electrically remodeled atria in the current RAP rabbits, which should be confirmed biologically as well as electrophysiologically in the future.

4.2. Comparison of AERP-prolonging effect of 6 antiarrhythmic drugs in the normal and electrically remodeled atrium

Based on the Guidelines for Pharmacotherapy of AF by the Japanese Circulation Society (1), potent Na+ channel blockers including pilsicainide and cibenzoline are recommended as pharmacological cardioversion for patients with paroxysmal AF lasting <48 h with no clinically significant structural disease, whereas only bepridil can be considered for patients with AF lasting >7 days with normal cardiac function and QT interval. This may imply that antiarrhythmic drugs being clinically effective in the acute phase of AF are not always available for the treatment of patients with persistent AF associated with pathophysiological remodeling of the atrium. In the present study, bepridil prolonged the AERP both in the control and RAP rabbits, whose extents were almost the same between the experimental groups, as shown in Fig. 2. Similar results were obtained by dl-sotalol, amiodarone and vernakalant in this study. On the other hand, ranolazine and tertiapin-Q prolonged the AERP in both experimental groups; however, the extent in the RAP rabbits was significantly greater than that in the control rabbits. These results suggest that rapid pacing-induced electrical remodeling effectively modified the prolonging effects of ranolazine and tertiapin-Q on the AERP in contrast to those of clinically available antiarrhythmic drugs, dl-sotalol, bepridil amiodarone and vernakalant. As shown in the Table 2, the 6 drugs essentially have anti-AF effects in the RAP rabbits. However, obvious relationship was not observed between prolongations of AERP and anti-AF effects. Since AF has been demonstrated to be caused by abnormal focal excitability as well as random reentry of multiple wavelets in animals and humans (1,3–5), Na+ channel-blocking properties of some drugs including amiodarone might counteract the burst pacing-induced AF associated with components of abnormal focal excitability.
Previous cellular electrophysiological experiments have revealed that an antiarrhythmic drug ranolazine suppresses the late \( I_{Na} \) and \( I_{Kr} \) with IC50 values of 5.9 and 11.5 \( \mu \)M, respectively, which are more potent than its effects on the peak \( I_{Na} \) and \( I_{Ca,L} \) (IC50: 294 and 296 \( \mu \)M, respectively) (12,13). Since ranolazine prolonged the QT interval, as shown in Table 3, it is estimated that the current dose of the drug (10 mg/kg) effectively inhibited the \( I_{Kr} \) as well as late \( I_{Na} \). The P-wave duration, roughly reflecting intra-atrial conduction time, was hardly affected by ranolazine, which can be explained by its weaker effects on the peak \( I_{Na} \) than the late \( I_{Na} \) and \( I_{Kr} \). Pharmacological inhibition of late \( I_{Na} \) generally abbreviates the action potential duration (14,15), which can theoretically counteract the component of \( I_{Kr} \)-inhibiting effect of ranolazine on the AERP. On the other hand, contribution of late \( I_{Na} \) is known to be greater in the longer action potential duration (14,15). Since the AERP was significantly abbreviated in the electrically remodeled atria, the integral of the late \( I_{Na} \) was estimated to be smaller in the RAP model, which may partly explain why ranolazine prolonged the AERP in the RAP rabbits more greatly than in the control animals.

Tertiapin-Q is an \( I_{K,ACh} \) blocker derived from bee venom, known as a useful peptide for investigating a therapeutic utility of \( I_{K,ACh} \) blockade (16). In this study, tertiapin-Q prolonged the AERP in both experimental groups, and the extent in the RAP rabbits was significantly greater than that in the control rabbits. A previous electrophysiological study has demonstrated that \( I_{K,ACh} \) is constitutively active in the isolated atrial cardiomyocytes from patients with long-term AF compared with non-AF patients (17), which was also supported by an experimental study using dogs with RAP (18). Thus, similar mechanisms might be involved in the atria of our RAP rabbit model. On the other hand, bepridil (19), amiodarone (20) and vernakalant (21) have been reported to suppress \( I_{K,ACh} \) with IC50 values of 2–10 \( \mu \)M, whose potencies were relatively similar to \( I_{Kr} \)-blocking effect of each drug. The reason is still unclear why AERP-prolonging properties of bepridil, amiodarone and vernakalant were different from that of tertiapin-Q. Since information is limited regarding affinities of the drugs used in this study for channels of \( I_{K,ACh} \) and constitutively-active \( I_{K,ACh} \) (9), this should be further investigated for discovering new type of anti-AF drugs.

### 4.3. Comparison of hemodynamic and electrophysiological effects of 6 antiarrhythmic drugs in the normal and electrically remodeled rabbits

In this study, bepridil, amiodarone, vernakalant and ranolazine decreased the mean blood pressure in both rabbit models, whereas \( dl \)-sotalol or tertiapin-Q hardly affected it, which are essentially in accordance with previous in vivo studies using dogs or rabbits (22–27). The atrial rate was significantly increased by tertiapin-Q in the control rabbits as well as RAP rabbits, which might be associated with counteraction of intrinsic parasympathetic nerve activity through its \( I_{K,ACh} \)-blocking property (28). Bepridil and amiodarone prolonged the P-wave duration in the control rabbits. Since it was not observed in the RAP rabbits, Na+ channel-blocking actions of these drugs in the atria might be altered by electrical remodelings. In contrast, vernakalant prolonged the P-wave in both animal groups in this study, which was essentially in accordance with previous studies (29,30). \( dl \)-Sotalol, bepridil, amiodarone, vernakalant and ranolazine prolonged the QT interval at the AERP-prolonging dose, which were in accordance with previous studies (23–25,31). Since antiarrhythmic drugs often exert some cardiovascular side effects at effective doses, discovery of drugs with more potent AERP-prolonging action in the remodeled atrium than normal atrium are expected for greater safety margin.

### 4.4. Study limitations

This study may partly provide information for the mechanisms of electrical remodeling in the RAP rabbit heart as well as impact on the drug development efforts aimed at improving existing antiarrhythmic drugs. The mechanisms of electrical and ionic remodeling during atrial tachycardia; namely, reduction of \( I_{Ca,L} \) and \( I_{Na} \) and increment of constitutive \( I_{K,ACh} \), have been demonstrated to be essentially similar between human AF and animal AF model (3–5,9–11). However, an earlier in vitro electrophysiological study has demonstrated that the AERP in rabbits is much shorter than that in human (87 ms vs 324 ms) and that sensitivity of drugs such as flecainide and quinidine to the AERP in rabbit is lower than that in human (32). Thus, caution should be taken in extrapolating our findings to AERP-prolonging effects in AF patients.

### 4.5. Conclusions

Rapid pacing-induced electrical remodeling effectively modified the prolonging effects of ranolazine and tertiapin-Q on the AERP in contrast to those of clinically available antiarrhythmic drugs, \( dl \)-sotalol, bepridil amiodarone and vernakalant. This understanding will be useful for prescribers to select antiarrhythmic drugs for AF patients with electrically remodeled atria.

### Conflicts of interest

We declare no conflict of interest.

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