Frequency-Dependent Antiarrhythmic Drug Effects on Postrepolarization Refractoriness and Ventricular Conduction Time in Canine Ventricular Myocardium in Vivo

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ABSTRACT
Both conduction time (CT) and effective refractory period (ERP), absolute and relative to action potential duration (APD), are major determinants of re-entry arrhythmia circuits. We compared the effects of 3 commonly used class I antiarrhythmic agents, lidocaine, mexiletine and quinidine, and of the combination of the latter 2, on APD, ERP, ERP/APD ratio and interventricular CT in 26 in vivo canine hearts. To assess also the frequency dependence of these effects, each measurement was made at multiple steady-state cycle lengths ranging from 600 to 250 msec. A modified contact electrode technique was used to measure both APD and ERP simultaneously and at the same left ventricular site. Interventricular CT was measured as the interval from the stimulus of right ventricular paced beats to the upstroke of the ensuing left ventricular action potential. Lidocaine did not change APD, ERP and ERP/APD ratio significantly at any basic cycle length. In contrast, both mexiletine and quinidine increased the ERP/APD ratio, with progressively greater effects toward shorter cycle lengths. The quinidine/mexiletine combination increased the ERP/APD ratio significantly more than either drug alone (cycle length 350 msec: 8.3 ± 2.2% quinidine; 17.6 ± 7.0% mexiletine; 35.3 ± 9.6% mexiletine/quinidine combination, P < .01 vs. quinidine, P < .05 vs. mexiletine). CT increased only with quinidine but not with mexiletine or lidocaine. Combination of mexiletine and quinidine caused no further slowing of conduction as compared to quinidine alone. Thus, although both ERP/APD ratio and CT are related to sodium channel conductance, drug effect on one parameter does not necessarily imply quantitatively similar effects on the other. This study demonstrates that effects of antiarrhythmic drugs on membrane excitability and conduction properties can be differentiated in vivo. This may be important for a more rational approach to antiarrhythmic drug therapy.

Antiarrhythmic efficacy of class I antiarrhythmic drugs commonly are ascribed to their ability to suppress both myocardial excitability and conduction velocity (Bigger and Hoffman, 1985; Bassett and Hoffman, 1971). An increase in the effective refractory period relative to APD may be especially effective in suppressing premature depolarizations (Bassett and Hoffman, 1971; Szekeres and Vaughan Williams, 1962), whereas slowing of impulse conduction may increase the tachycardia cycle length. However, slowing of conduction does not necessarily prevent re-entrant tachycardias but may actually facilitate their onset by permitting the leading impulse to propagate despite an increased ERP ahead of it (Frame and Hoffman, 1984; Wit et al., 1972).

Although effects of antiarrhythmic drugs on action potential characteristics and conduction properties have been studied extensively in in vitro cardiac preparations, relatively little is known about their electrophysiologic effects in the intact, in vivo heart. Especially unexplored is the in vivo effect of antiarrhythmic drugs on APD and ERP, and on the ratio between the two (ERP/APD ratio), because it has not been possible to measure APD and ERP at the same site in an intact heart. Isolated and artificially perfused preparations may have altered electrophysiologic properties in response to individual antiarrhythmic drugs, and may not reflect the pharmacodynamic situation of the in vivo myocardium. We have recently developed a method to record monophasic action potentials and determine ERP at the same time and the same site in the in vivo beating heart, permitting calculations of the ERP/APD ratio with a precision similar to in vitro studies (Franz and Costard, 1988).

In light of the uncertainties about differential antiarrhythmic drug effects in vivo, we used this method to quantify, in an open chest canine preparation, the effects of three commonly used antiarrhythmic drugs (lidocaine, quinidine, mexiletine and...

ABBREVIATIONS: APD, action potential duration; ERP, effective refractory period; MAP, monophasic action potential; CT, conduction time; S1, stimulus of paced beats; S2 (S3,S4), 1st (2nd,3rd) extrastimulus.
combination of the latter two), on ERP, APD, ERP/APD ratio and on interventricular CT. To also allow comparison of use-dependent characteristics of our in vivo results with previously reported in vitro data, we extended our measurements over a wide range of steady-state cycle lengths.

Methods

Mongrel dogs of either sex weighing 10 to 30 kg were premedicated with morphine sulfate (2 mg/kg) i.m., anesthetized with urethane (625 mg/kg) and alpha chloralose (80 mg/kg) i.v. with 10% of these initial doses every hour and paralyzed with 0.03 mg/kg succinylcholine IV. Auffed endotracheal tube was inserted and the animals were ventilated with room air using a Harvard respirator. Arterial blood specimens were analyzed frequently using a Corning blood gas analyzer (model 165), and tidal volume and respiratory rate were adjusted to maintain the level of arterial oxygen pressure above 80 mm Hg and the pH between 7.35 and 7.45. Polyethylene catheters were placed in the femoral artery for continuous arterial pressure monitoring and in the jugular vein for drug infusion. Hearts were exposed through a left thoracotomy and suspended in a pericardial cradle. Four limb leads were attached for ECG monitoring. MAP were preamplified using a high input impedance, d.c.-coupled amplifier (Grass Instruments P 16). Aortic pressures were recorded using a Statham P 23 Db transducer. The ECG leads, aortic pressure and the action potentials were recorded simultaneously by use of a multichannel electrostatic recorder (Gould ES 1000) with a frequency response of 0 to 5000 Hz.

Hearts were paced with basic stimuli of 1-msec duration and twice diastolic threshold strength through a pair of needle electrodes placed on the right ventricular free wall. Monophasic action potentials were recorded using the silver/silver chloride contact electrode probe, which was positioned on the left ventricle. As described earlier (Franz and Costard, 1988) the electrical dipole was connected to both a preamplifier for recordings of action potentials and to a stimulus generator. Thereby the extrastimuli for determination of ERP were applied through the same pair of electrodes used for action potential recordings, allowing simultaneous measurement of APD and ERP at the same myocardial site. ERP was determined twice at each cycle length.

Figure 1 illustrates the method of measuring APD, ERP and interventricular CT: hearts were paced continuously with basic drive stimuli (S1) from a right ventricular epicardial site until all electrophysiologic parameters had reached steady state. APD was recorded with the MAP electrode from a left ventricular epicardial site and measured at the level of 90% repolarization (APD90). (In the subsequent text, APD refers to APD90 unless cited.) The ERP was measured at the same site at which the APD was determined, using the following approach. Every 12 regularly paced beats (S1), an extrastimulus (S2) was applied through the same electrode pair that recorded the MAP, without ensuing pause. Using the MAP upstroke of the last regularly paced beat as the time of basic excitation, the ERP was defined as the minimum interval after the MAP upstroke at which a twice diastolic threshold stimulus applied at the same site failed to elicit a propagated response (panel A). Interventricular CT of steady-state beats was measured from the stimulus artefact of basic paced beats (S1, applied to the right ventricle) to the upstroke of the corresponding action potential (left ventricular site). Because this evaluation of CT is reliable only as long as the activation pathway remains unchanged, the morphology of the QRS complex in the surface ECG was observed carefully, and all complexes that suggested aberrant conduction were excluded from data analysis.

Study protocol. Measurements of ERP, APD and CT were obtained over a range of basic cycle lengths between 600 and 250 msec, starting with the longest cycle length to overdrive the spontaneous rhythm and continuing in decremental steps of 50 ms. To ensure steady state, each cycle length was maintained constant for at least 2 min before measurements were started.

After obtaining measurements in the drug-free state, the same protocol was repeated after administration of either lidocaine, mexiletine or quinidine. Drug dosages were as follows: lidocaine (N = 8): bolus injection of 2 mg/kg, followed by a continuous infusion at a rate of 0.07 mg/kg/min (Kupersmith, 1979); quinidine gluconate (N = 11): bolus injection of 3.85 mg/kg, followed by a continuous infusion at a rate of 0.28 mg/kg/min (Goldman et al., 1983) and mexiletine (N = 10): bolus injection of 2 mg/kg, followed by an infusion of 0.1 mg/kg/min for 30 min and thereafter by 0.02 mg/kg/min. In addition the effect of combined infusion of mexiletine and quinidine was tested at the same dosages that were used for single drug infusion (N = 10).

In all experiments measurements were started after an equilibration period of 30 min constant infusion. Blood samples for determination of drug serum concentration were drawn after 30 and 90 min of constant infusion (American Bioscience Laboratories). Experiments with drug levels not in the therapeutic range [2-5 μg/ml of quinidine (Halkin et al., 1973), 0.75-2.0 μg/ml of mexiletine (Woosley et al., 1984) and 2-6 μg/ml of lidocaine (Gianelly et al., 1967)] or with values which showed that steady state was not achieved were excluded from the analysis. Stimulus thresholds were reassessed after drug administration and, if necessary, stimulus output was adjusted to twice diastolic threshold at the longest basic cycle length (usually 600 msec).

Presentation of data and statistical analysis. APD was averaged over the five consecutive responses which preceded S2. The variance between these individual APD determinations was less than 2% or 5 msec, respectively. APD and ERP were expressed in milliseconds and, after drug infusion, as percent change vs. control. Group data are presented as mean ± S.E.M. A P value of less than .05 was considered statistically significant. To assess the significance of frequency related changes, two-factorial analysis of variance for repeated measures was used with an F test for interaction. If significant difference (P < .05) was detected, Duncan’s Multiple Range test was used to analyze paired data. The significance of the drug effect at a given cycle length was determined by a paired t test comparing the base line values and the values obtained after drug infusion in the same animal. To compare drug effect of quinidine with that of the drug combination (tested in different animals), two-tailed unpaired t test was used.

Results

Drug plasma concentrations. Among the experiments that verified steady-state conditions mean plasma concentrations during single drug infusion were as follows: lidocaine, 3.4 ± 0.7 μg/ml; mexiletine, 1.7 ± 0.5 μg/ml; quinidine, 3.3 ± 1.1 μg/ml. Combined drug infusion did not alter plasma concentrations of either drug (mexiletine, 1.9 ± 0.3 μg/ml; quinidine, 3.2 ± 1.5 μg/ml).

APD and ERP in the drug-free state. As shown previously (Franz and Costard, 1988), in the drug-free state APD shortened linearly as cycle length was shortened. Refractory periods decreased toward shorter cycle lengths in a parallel fashion, indicating close correlation between repolarization and refractoriness in the drug-free state.

Drug effect on APD and ERP. Figure 2 depicts the drug effect on APD and refractoriness in normalized values, e.g., percentage change from base line. The only significant effect of lidocaine was a slight shortening of APD at long cycle lengths. Quinidine increased APD uniformly (11-13 msec). In contrast, the effect on refractoriness was strongly rate-dependent. At cycle lengths of 450 to 600 msec quinidine prolonged ERP by a small amount (15-20 msec), only slightly more than the concomitant increase in APD. However, at shorter cycle lengths quinidine prolonged ERP progressively more, up to a maximum increase of 52 ± 10 msec at a cycle length of 250 msec (P < .001).

Like lidocaine, mexiletine shortened APD significantly at long cycle lengths. However, mexiletine’s effect on ERP resem-
abled that quinidine: mexiletine prolonged ERP in a rate-dependent fashion up to a maximum of 47 ± 14 msec at a cycle length of 300 msec (P < .01). During steady-state pacing at a cycle length of 250 msec, refractoriness exceeded the basic coupling interval in 3 of 10 experiments so that capture occurred only intermittently, demonstrating marked drug-induced prolongation of ERP.

The combination of mexiletine and quinidine increased APD by 6 to 9 msec, which was less than the effect of quinidine alone and significant only at cycle lengths ≤ 300 msec. In contrast to APD, ERP was increased significantly more than with either mexiletine or quinidine alone. As during single-drug infusion the prolongation of ERP was strongly rate-dependent, increasing from 21 to 28 msec at cycle lengths between 600 and 450 msec to a maximum of 65 ± 18 msec at a cycle length of 350 msec (P < .005 vs. base line; P < .02 vs. quinidine; P < .02 vs. mexiletine). The marked increase of ERP by the drug combination on postrepolarization refractoriness was further demonstrated by the fact that failure to capture during steady-state pacing started to occur at longer cycle lengths (3 of 9 experiments at a cycle length of 300 msec) and in more experiments (6 of 9 experiments at a cycle length of 250 msec) than with mexiletine alone.

**Drug effect on ERP/APD ratio.** Figure 3 summarizes the drug effect of the three tested agents, and of the mexiletine/quinidine combination on ERP/APD ratio. In the drug-free state, ERP/APD ratio was constant over the entire range of tested cycle lengths, indicating close, rate-independent correlation between repolarization and refractoriness. Averaged from all 26 experiments, ERP was 10 msec shorter than APD at 90% repolarization, corresponding to an ERP/APD ratio of 0.95 ± 0.01. Lidocaine did not affect the ERP/APD ratio significantly, although there was a trend to increase this relationship due to shortening of APD at long cycle lengths and a lengthening of ERP at short cycle lengths as compared to baseline. In contrast, both mexiletine and quinidine caused a marked increase in ERP/APD ratio at short cycle lengths, reflecting the drugs' rate-dependent prolongation of ERP. With both agents, ERP/APD ratio increased to values greater than 1, indicating that refractoriness was prolonged beyond full repolarization and true postrepolarization refractoriness was produced. The combination of mexiletine and quinidine again
increased the ERP/APD ratio rate-dependently, reflecting the effects from individual drugs. The combination of these agents with opposite effect on APD and similar effect on ERP resulted in an increase of ERP/APD ratio that was significantly larger than that produced by either drug alone: at a cycle length of 350 msec for example, ERP/APD ratio was 1.28 ± 0.11, compared to 1.10 ± 0.07 with mexiletine (P < 0.04 vs. combination) and 1.03 ± 0.03 (P < 0.01 vs. combination) with quinidine alone.

**Drug effect on conduction time.** Complete data on interventricular conduction time (after excluding data where changes in QRS complexes suggested aberrant conduction) were obtained in five dogs after lidocaine infusion, in five dogs after quinidine infusion, in seven dogs after mexiletine infusion and in six dogs after combined infusion of mexiletine and quinidine (fig. 4). In the drug-free state, conduction time of steady-state beats was constant over the entire range of cycle lengths with a mean of 93 ± 4 msec. Among different experiments, mean conduction time ranged from 72 ± 2 to 100 ± 2 msec. Both lidocaine and mexiletine did not prolong conduction time significantly. In contrast, quinidine prolonged conduction time, the effect increasing slightly with shorter cycle lengths up to a maximum of 17 ± 7 msec at a cycle length of 250 msec. The quinidine-mexiletine combination caused a similar prolongation of CT, not significantly more than quinidine alone (cycle length 250 msec: 20 ± 4 msec).

Figure 5 shows for two basic cycle lengths, 450 and 350 msec, respectively, a comparison between the drug effect on CT and on ERP/APD ratio, expressed as percent change from base line. For quinidine the percent increase of ERP/APD ratio was accompanied by a comparable relative prolongation of CT (difference between percent change ERP/APD ratio vs. CT not significant). In contrast, mexiletine increased ERP/APD ratio without a concomitant slowing of conduction [difference between percent change ERP/APD ratio vs. CT P < .05 (cycle length 550 msec) to P < .005 (cycle length 300 msec)]. Although the combination of mexiletine and quinidine increased ERP/APD ratio significantly more as compared to either single drug alone, the combination did not increase conduction time further beyond the amount seen with quinidine alone.

**Discussion**

This *in vivo* monophasic action potential study shows that the antiarrhythmic agents lidocaine, quinidine and mexiletine in plasma concentrations comparable to those used clinically produce distinctive changes in both APD and ERP which are similar to, and thus corroborate the implications of, previous *in vitro* data. In those earlier studies in excised myocardial tissues quinidine also prolonged APD (Roden and Hoffman, 1985; Varro et al., 1986; Burke et al., 1986; Campbell, 1983), lidocaine and mexiletine shortened APD and these action potential shortening effects were most marked at long cycle lengths (Burke et al., 1986; Varro et al., 1985a,b). Also in keeping with previous *in vitro* studies (Rodent al., 1987), the combined infusion of quinidine and mexiletine reduced the APD prolonging effect provided by quinidine alone.

The *in vivo* effect of the tested agents on ERP relative to repolarization has not yet been explored. *In vitro* data on the drugs' effect on ERP/APD ratio are controversial. For therapeutic concentrations of all three an increase of ERP/APD ratio (Burke et al., 1986; Campbell, 1983; Varro et al., 1985a) as well as no effect (Burke et al., 1986; Campbell, 1983; Duff et al., 1986) has been demonstrated. In the present study the
effect on ERP relative to APD varied characteristically with the individual drugs. Although lidocaine did not affect ERP or the relationship between ERP and APD, quinidine produced greater increases in ERP than APD, thus increasing the ERP/APD ratio. Mexiletine resembled lidocaine in its effect on APD, but was more like quinidine in its effect on ERP, a finding that corroborates a previous in vitro study (Burke et al., 1986). As a consequence of its opposing effect on ERP and APD, mexiletine increased the ERP/APD ratio markedly.

Because sodium channel blocking drugs may increase excitation threshold even in the absence of use-dependence, stimulus output needed to be increased in some experiments after drug administration. Although increased stimulus strength shortens ERP under normal (drug-free) conditions, this was not the case in the postdrug state. Even with stimulus output adjusted to twice end diastolic threshold, prolongation of ERP was observed even at the longest basic cycle length. With decrease in cycle length, increase in ERP relative to APD became progressively more apparent. If increase in stimulus output caused any error in the comparison between predrug and postdrug state, it would be an under-estimation of the frequency dependency observed.

The differential effect on ERP and APD became even more obvious when the frequency of stimulation was raised. Compared to base line, quinidine and mexiletine prolonged ERP progressively toward shorter cycle lengths, a finding that has previously been noted in vitro (Nattel and Zeng, 1984). In contrast to previous in vitro data (Burke et al., 1986; Varro et al., 1985a; Nattel and Zeng, 1984), we did not find ERP shortening with lidocaine. However, those in vitro studies measured lidocaine's effects on ERP only at cycle lengths longer than those tested in our study. A previous in vivo canine study, which tested a single cycle length of 350 msec, also found no significant change in ERP during lidocaine infusion (Kupersmith, 1979).

The combined infusion of mexiletine and quinidine, using the same concentrations as during single drug infusion, caused a rate-dependent prolongation of ERP and an increase in ERP/APD ratio to a degree that was not achieved with either drug alone. There is no previous study which tested this drug combination’s effect on ERP/APD ratio or has the effect on refractoriness been studied over a range of steady-state cycle lengths. One study on isolated perfused rabbit hearts driven at a single cycle length of 1000 msec also found additive increase in refractoriness during drug combination (Duff et al., 1986). Duff et al. (1987) examined in a clinical study the effects of mexiletine, quinidine and of their combination on ERP using single (S2), double (S3) and triple (S4) extrastimuli, and provided some previous evidence for drug-induced, rate-dependent effects of antiarrhythmic drugs on ERP. These authors found that quinidine prolonged ERP for all three extrastimuli, whereas mexiletine lengthened only S4-ERP, and quinidine-mexiletine combination caused additive prolongation only of S4-ERP. The present study confirms this effect over a range of steady-state cycle lengths and also distinguishes between ERP changes that accompany APD changes and those that do not.

Consistent with previous in vitro and in vivo studies which
Fig. 4. Drug effect on interventricular CT as a function of steady-state cycle length. The open circles represent data during base line, the closed circles those after drug infusion as indicated. * P < .05 vs. base line.

Fig. 5. Comparison between drug effect on interventricular CT and ERP/APD ratio, expressed as percent change from base line. * P < .05% change of drug effect on ERP/APD ratio vs. CT.
assessed ventricular conduction as His-bundle CT (Davis et al., 1986; Gang et al., 1985) or as CT between closely spaced bipoles on the epicardial surface (Bajaj et al., 1987), we found that in the drug-free state CT is constant over a large range of cycle lengths. The three antiarrhythmic agents tested in this study produced differential effects on CT. Lidocaine did not change interventricular conduction over the range of cycle lengths tested. To avoid hypotension or ventricular fibrillation, we did not attempt to shorten steady-state pacing cycle length below 250 msec. This might explain the discrepancy to a recent in vivo canine study, which found lidocaine to increase His bundle CT, but only when cycle length was decreased below 250 msec (Gang et al., 1985).

Furthermore, the findings of our study are in agreement with clinical observations that therapeutic concentrations of lidocaine do not slow ventricular conduction at normal heart rates (Bekheit et al., 1973; Rosen et al., 1970). In keeping with earlier in vivo studies measuring intraventricular CT (Wallace et al., 1966) and epicardial conduction (Bajaj et al., 1987), we found that quinidine slows CT over a large range of cycle lengths. Our data on the effect of mexiletine are only partly in agreement with a recent in vivo study which tested a range of cycle lengths between 250 and 1500 msec (Bajaj et al., 1987); these investigators found no effect of mexiletine at slow rates but significant, orientation-dependent slowing of conduction at cycle lengths shorter than 400 msec, cycle lengths at which we did not see any effect of mexiletine.

The present study demonstrates differential drug effect on ERP/APD ratio and CT; with quinidine the increase of ERP/APD ratio was paralleled by a comparable increase of interven- tricular CT, whereas mexiletine caused marked increase in ERP/APD ratio without concomitant slowing of CT. The combination of mexiletine and quinidine caused a significantly larger increase in ERP/APD ratio than did either drug alone but did not slow CT further as compared with quinidine alone.

These findings may be explained by different recovery kinetics from phasic sodium channel block with ERP/APD ratio CT reflecting sodium channel block at different times during dias- tole. Drug-induced increase in ERP/APD ratio indicates suppression of excitability, and thus sodium channel block at the end of the action potential, i.e., early diastole, because ERP is determined by premature stimuli. Drug-induced slowing of conduction, on the other hand, reflects sodium channel block at late diastole, i.e., the time at which the next steady-state depolarization occurs. For lidocaine the recovery time constant has been reported to be 90 to 152 msec (Varro et al., 1985b; Davis et al., 1986). This is shorter than the range of APD measured in this study and may explain why lidocaine did not increase the ERP/APD ratio. In contrast, for quinidine with a reported recovery constant of 4 to 8 sec (Varro et al., 1985b; Roden et al., 1987; Hondeghem and Katzung, 1977), sodium channel block would persist at similar magnitudes throughout the cardiac cycle, resulting in quantitatively similar increases in ERP/APD ratio and CT. The recovery time constant for mexiletine has been measured at intermediate values of 200 to 500 msec (Rodent al., 1987; Bajaj et al., 1987), and this may explain why mexiletine increases the ERP/APD ratio, espe- cially at high heart rates, with less effect on CT.

CT not only is affected by changes in sodium channel con- ductance but also by changes in cell coupling (De Mello, 1976; Spach et al., 1981). The latter has been shown to be direction- dependent so that sodium channel block results in dispropor- tionate longitudinal conduction slowing (Bajaj et al., 1987).

This may be an additional factor why changes in ERP/APD ratio and CT, though both dependent on sodium channel avail- ability, are not necessarily quantitatively related.

Although the morphology of QRS complexes was observed carefully and all data suggesting aberrant conduction excluded from analysis, it cannot be ruled out with absolute certainty that changes in the route of propagation unnoticeable in the surface ECG did not occur (Spach et al., 1981). However, the fact that the position of the right ventricular pacing electrodes and the left ventricular MAP probe remained constant through- out the study protocol, which often included multiple drugs, makes it unlikely that a change in the route of impulse propa- gation affected our measurements of CT systematically.

This study demonstrates that simultaneous recording of APD and ERP by our modified MAP contact electrode technique allows one to measure the effects of antiarrhythmic drugs on the relationship between excitability and repolarization (ERP/ APD ratio), and the rate dependence of such effects, in vivo. As discussed above, such in vivo data correspond well with specific electrophysiologic drug effects previously established in vitro. Application of this technique in the clinical electro- physiologyp laboratory is feasible (Liem et al., 1987) and may provide a means for quantitating and characterizing the electro- physiologic effects of antiarrhythmic drugs in the human heart.

It has long been implicated that drug-induced prolongation of refractoriness, absolute and relative to APD, is an important factor for antiarrhythmic drug efficacy (Bassett and Hoffman, 1971). However, prolongation of refractoriness is of value in suppressing arrhythmias only as long as the other major deter- minant of re-entry arrhythmias, myocardial conduction velocity, is not decreased to a similar degree (Frame and Hoffman, 1984; Wit et al., 1972). Our finding that the combination of mexiletine and quinidine produces postrepolarization refracto- riness without equal slowing of conduction may explain the favorable antiarrhythmic efficacy of this drug combination as compared to effects of either drug alone (Duff et al., 1983; Greenspan et al., 1985). It should be of significant interest to evaluate the efficacy of other antiarrhythmic drugs, and of their combinations, under this new and clinically approachable as- pect.

References


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