Pre-procedural Clinical Parameters Determining Peri-Mitral Conduction Time during Mitral Isthmus Line Ablation

Running title: Miyazaki et al.; Peri-Mitral Conduction Time during Linear Ablation

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Abstract:

Background - Achievement of complete conduction block across left mitral isthmus (MI) is challenging. Anticipation of peri-mitral conduction time (PMCT) associated with MI block may expedite this procedure. We evaluated the relationship between the preprocedural variables and the quantum of PMCT in patients with bidirectionally blocked MI.

Methods and Results - 1) We reviewed clinical and echocardiographic parameters in 290 consecutive patients with confirmed bidirectional MI block during atrial fibrillation (AF) ablation. PMCT was defined as the temporal delay to the latest of the double potentials on the line of block while pacing posteroseptal to it in the left atrium (LA). LA size and type of AF significantly influenced PMCT in multivariate analysis. A cumulative score based on LA size (0≤45 mm; 1>45 mm) and type of AF (0=paroxysmal; 1=non-paroxysmal), ranged from 0 to 2. PMCT was directly correlated to the cumulative score (0: 169 ms (n=78, 95% confidential interval (CI) 156-181), 1: 187 ms (n=103, 95%CI 178-196), 2: 209 ms (n=109, 95%CI 200-217)). In 61 patients who underwent AF ablation twice, the difference between two PMCT values was less than 30ms in 75% patients. 2) Another consecutive 143 patients with and without MI block after at least 15 minutes of radiofrequency application were analyzed. Perimitral conduction delay (PMCD) <130ms ruled out bidirectional MI block. PMCD >173ms predicted bidirectional block with an accuracy of 86%.

Conclusions - LA size and AF type significantly influence PMCT in patients undergoing successful MI ablation. These parameters can be used to predict the time-value associated with MI block, pre-procedurally.

Key words: mitral isthmus, linear ablation, atrial fibrillation, catheter ablation, perimitral conduction time
**Introduction**

In recent years, catheter ablation is increasingly and widely undertaken for the treatment of atrial fibrillation (AF) in the patients who do not respond to antiarrhythmic drug therapy.[1-4] Several studies have described the additional benefit of mitral isthmus (MI) line in persistent AF and macroreentrant ATs.[5-8] MI linear ablation extends from the lateral mitral annulus anteriorly to the left pulmonary vein (PV) posteriorly.[5.6] Since incomplete block increases the risk of perimital macroreentrant AT, the achievement of complete bidirectional conduction block is recommended as the endpoint of MI ablation by the HRS/ESC/ECAS consensus statement on the catheter ablation of AF.[9.10]

Assessment of conduction block across MI is performed using pacing technique.[5.11] Although it is possible to continuously monitor trans-isthmus conduction during application of the lesion across MI, it is difficult to predict the quantum of delay which signifies complete block. Because of interindividual variation in the perimital conduction velocity and the circumference of the mitral annulus, there cannot be a fixed value of peri-mitral conduction time (PMCT) signifying complete block across MI. We hypothesize that the estimate of PMCT evaluated using clinical parameters before the procedure could help reduce the procedural time. A large number of patients with confirmed bidirectional MI conduction block were analyzed.
Methods

Consecutive MI linear ablation procedures in the context of AF ablation between July 2004 and November 2009 were included in this study.

AF was defined as paroxysmal (spontaneously terminating and sustained less than 7 days), persistent (sustained beyond 7 days or lasting less than 7 days but necessitating cardioversion) and long-lasting persistent (continuous AF lasting longer than 1 year) according to the HRS/EHRA/ECAS 2007 Consensus Statement on Catheter and Surgical Ablation of AF.[10] All patients had given written informed consent prior to the procedure.

Electrophysiological Study

All anti-arrhythmic medications, with the exception of amiodarone, were discontinued at least five half-lives prior to ablation. All patients were anti-coagulated with warfarin for at least 1 month before the procedure (target International Normalized Ratio 2–3), and therapeutic anti-coagulation was maintained with intravenous or low molecular weight heparin following warfarin discontinuation 3 days prior to the intervention. Transesophageal echocardiography was performed within 48 h prior to the procedure to exclude LA thrombus. Warfarin was restarted on the day of the procedure and effective anti-coagulation maintained with heparin until the INR was greater than 2.0.

Surface electrocardiogram and bipolar endocardial electrograms (filtered from 30 to 500
Hz) were continuously monitored and stored on a computer-based digital amplifier/recorder system (Labsystem Pro, Bard EP, Lowell, MA). Electrophysiological study was performed in the fasting state using mild sedation. The following catheters were introduced via the right femoral vein: (i) a deflectable quadripolar or decapolar catheter (5-mm electrode spacing, Xtrem, ELA Medical, France) positioned within the coronary sinus (CS) with the distal electrode positioned at 4 o’clock along the mitral annulus in the 30° left anterior oblique radiographic projection; (ii) a 10 pole, fixed-diameter (20mm) circumferential mapping catheter to guide pulmonary vein (PV) isolation (Lasso; Biosense-Webster, Diamond Bar, CA), introduced with the help of a long sheath (Preface multipurpose, Biosense-Webster or SLO, St. Jude, MN, USA) which was continuously perfused with heparinized saline; (iii) a 3.5 mm externally irrigated-tip quadripolar ablation catheter (5-mm inter-electrode spacing, Thermocool, Biosense-Webster, Diamond Bar, CA).

A single trans-septal puncture was performed in the anteroposterior radiographic projection with pressure monitoring. LA access was confirmed by an appropriate atrial pressure waveform and contrast opacification of the LA. The circumferential mapping catheter was introduced into the LA trans-septally using the sheath which was later withdrawn into the right atrium to facilitate the passage of the ablation catheter to the LA through the same transseptal puncture site. Following trans-septal puncture a bolus of 50 IU/kg of heparin was administered and repeated only if the procedure lasted beyond 4 hours.
Catheter Ablation

PV isolation was performed using radiofrequency (RF) application to eliminate electrograms around the ostia under the guidance of a circumferential mapping catheter positioned inside the PV. In the patients with persistent AF despite PV isolation, electrogram-based ablation was performed at the sites showing characteristic electrogram previously described.[1,2] Ablation at these atrial sites was performed for 20 to 60 seconds to achieve prolongation of local AF cycle length. If AF continued after PV isolation and electrogram-based ablation, linear ablation at the most cranial portion of the LA roof was performed with the end point of elimination of local electrograms.[12]

Linear ablation at the MI was performed in patients in whom AF persisted after the above mentioned steps were undertaken, or if peri-mitral AT was diagnosed. During AF, ablation was carried out on an anatomical basis with the end point being elimination of local electrograms using 30 to 35 W power. Radiofrequency application started at the lateral mitral isthmus (A: V electrogram amplitude ratio of approximately 1:1) and was extended posteriorly to the ostium of the left inferior PV. During peri-mitral AT or distal CS pacing, it was often necessary to extend the line of ablation to the base of the LA appendage (LAA) or to ablate inside the CS (with power upto 25 W) to eliminate residual gaps. After restoration of sinus rhythm, assessment of bidirectional conduction block was made as previously
described (Figure 1).[5] Briefly, pacing on one side of the MI linear ablation and simultaneous recording of the electrograms on the other were undertaken as close as possible to the line of block. Electrical block was differentiated from slow conduction by differential CS pacing.[11] Pacing distal bipoles on the CS catheter resulted in electrogram recording across line of MI linear ablation later than that during more proximal bipole pacing on the CS catheter (Figure 1A.B). Later, pacing laterally across the line of MI ablation resulted in proximal to distal activation of the CS (Figure 1C). Widely separated, equidistant, local double potentials along the length of the linear ablation were often observed (Figure 2).

PMCT was evaluated after validation of the conduction block across the MI. It was measured by recording temporal delay to the latest part of double potentials on the line of block while pacing just septal to the line of block in the LA at a cycle length of 600 ms (Figure 3).[13] During the procedure, antiarrhythmic drugs were not used.

Analysis of Peri-Mitral Conduction Time and pre-procedural variables

Three hundred and fifty one consecutive MI linear ablation procedures on 290 patients wherein bidirectional MI block was confirmed during AF ablation were included in this study. Preprocedural clinical and echocardiographic parameters were analyzed for any association with PMCT value obtained in patients with bidirectional block including age, gender, structural heart disease, LA size, left ventricular function, AF type and use of amiodarone.
Regarding amiodarone, the drug was considered to have been used only when the patients who were on amiodarone therapy continued to take it within last 3 months of the procedure.

Stability of Peri-Mitral Conduction Time between two separate procedures

Among 290 patients with bidirectional MI block, 61 patients underwent two ablation procedures. PMCT was evaluated at two separate procedures to assess its stability over a period of time between the two procedures.

Comparison of Peri-mitral conduction delay between patients with and without block

Furthermore, we also analyzed another 143 consecutive patients who underwent more than 15 minutes of RF application for MI ablation. These included the patients with and without MI block. Perimital conduction time was measured as described above. However, since this group also included patients without MI block, we used the terminology ‘perimiral conduction delay’ to distinguish it from ‘PMCT’ which was used restrictively for the previous group of 290 patients with confirmed MI block.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation. Comparison between groups was performed with the Student’s t-test or the Wilcoxon Rank-Sum test (for
non-normal data distribution), and 95% confidential interval (CI) was presented. Categorical variables are reported as number and percentage and are compared using the Fisher’s exact test. The paired nature of the data was compared using a paired t test for continuous variables and a McNemar test for the categorical variable.

To find the pre-procedural parameters associated with PMCT, multiple linear regression model, in which all variables which were significant in a univariate regression at p<0.2 were entered in the model, but only retained when significant at p<0.05. The cut off values of 45mm for LA size was chosen by considering the clinical significance and average/median LA size in the population. A point score was obtained using the relative magnitude of the regression coefficients rounded to a whole number. A one-way ANOVA was used to indicate the significance of the association between cumulative point score and PMCT.

The stability of the PMCT was examined using a Bland and Altman plot.

The peri-mitral conduction delay in the patients with and without block was compared, and a cutoff point was evaluated. The optimal cutoff point was chosen as the combination with the highest sensitivity and specificity using receiver-operator characteristic (ROC) curve in each group. A 95% CI was presented with the area under curve (AUC) in each score group. All tests were two-tailed and statistical significance was established at P < 0.05.

Results
Patient Characteristics

The patient characteristics are shown in Table 1. There were 290 consecutive patients (mean age 58± 10 years, 243 males, paroxysmal/ persistent/ long-lasting persistent= 87/75/128) with a total 351 procedures (index/second procedure for MI line ablation= 290/61) admitted for drug refractory symptomatic AF or AT in the context of prior AF ablation.

Preprocedural variables and Peri-mitral Conduction Time

The mean PMCT was 191 ± 46ms. Univariate analysis showed that LA size (p<0.0001), long-lasting persistent/persistent AF (p<0.0001), age (p=0.001), left ventricular ejection fraction (p=0.054) and use of amiodarone (p=0.002) significantly influenced the PMCT in patients with bidirectional MI block. On the other hand, gender (p=0.327), and structural heart disease (p=0.288) had no such influence. The multiple linear regression model, in which all significant variables in univariate regression were entered showed that LA size (p=0.025) and long-lasting persistent/persistent AF (p=0.003) were retained as the significant variables and that left ventricular ejection fraction (p=0.967) and age (p=0.443) were not. We assigned a numerical value to each of the significant factors as mentioned here – LA size (0≤45 mm; 1>45 mm) and AF type (0 = paroxysmal; 1 = non-paroxysmal). A mean PMCT in the patients with score 0, 1 and 2 were 169 ms (n=78, 95% confidential interval (CI) 156-181), 187 ms (n=103, 95% CI 178-196), and 209 ms (n=109, 95% CI 200-217). PMCT significantly
increased with increase in the cumulative parametric value (p<0.0001).

**Stability of Peri-Mitral Conduction Time between two separate procedures**

PMCT could be re-evaluated during a separate procedure in 61 patients (mean age 57 ± 10 years, 53 males, paroxysmal/ persistent/ long-lasting persistent =16/9/36) who underwent two ablation procedures, mean 10 ± 9 months apart. There was no significant difference in the LA size (46.3 ± 7.6 vs. 45.9 ± 8.5mm, p= 0.706) and amiodarone use (32.9% vs. 27.9%, p=0.450) determined at the index and second procedures. The mean PMCT did not change significantly over the whole population. In individual patients, the difference of PMCT between 1st procedure and 2nd procedures was less than 30ms in about 75% patients (Figure 4).

**Comparison of peri-mitral conduction delay between the patients with and without block**

Peri-mitral conduction delay was evaluated in 143 consecutive patients (mean age 58 ± 10 years, 120 males, paroxysmal/ persistent/ long-lasting persistent =40/56/47) with and without block. Complete block was achieved in 89 (62%) patients with 24±9 min of RF application from the endocardium and 4±3 min from the epicardium. The mean peri-mitral conduction delay was significantly higher in patients with block than without block (187 (95% CI: 177-196) vs. 123 ms (95% CI: 111-135), p<0.0001). Patients with higher cumulative parametric score had a higher peri-mitral conduction delay value than those with lower scores.
(Fig. 5). Overlapping values of peri-mitral conduction delay between both the groups was observed, however none of the patients with less than 130 ms of peri-mitral conduction delay demonstrated complete conduction block. For the association between the peri-mitral conduction delay value and complete MI block, the AUC was found to be 0.885. The optimal cutoff point for the PMCT value predicting MI block was 173 ms (sensitivity 90 %, positive predictive value 88 %, specificity 80%, accuracy 86 %). The AUC was 0.952, 0.950, and 0.818 for the patients with cumulative parametric scores of 0, 1, and 2 respectively. The optimal cutoff point for the PMCT value associated with block was 147, 167 and 185 ms in the patients with cumulative parametric scores of 0, 1, and 2 respectively (sensitivity/specificity -%: 100/ 90, 94/89 and 97/67 respectively) (Fig. 6).

**Discussion**

The present study demonstrates 1) easily identifiable pre-procedural parameters which impact the PMCT in presence of MI block, 2) stability of PMCT between the two ablation procedures, and provides 3) a typical range of peri-mitral conduction delay values which can be useful during MI ablation in patients with various different AF-related clinical characteristics.
Several studies on AF ablation have described the additional benefit of the MI linear ablation.[1.5.6] Furthermore, MI linear ablation has to be undertaken for peri-mitral tachycardia frequently observed after the termination of AF.[7] However, despite the use of three-dimensional electroanatomical mapping systems, robotic and remote magnetic navigation systems and irrigated-tip ablation catheter, creation of complete line of block across the MI remains challenging.[5.6] The tissue thickness, the anatomical complexity, the catheter instability and the presence of myocardial sleeves connecting the LA to the CS have been described as the major reasons of difficulty in achieving transmural lesion at the MI.[5.6.14-17] It is also possible that blood flow within the circumflex coronary artery and the coronary sinus prevent transmural lesions by acting as epicardial heat-sinks.[18]

The method for assessing complete conduction block across the MI involves mapping of the endocardial and the epicardial activation around the mitral annulus during both the distal CS and the LAA pacing.[5.11] Widely split double potentials all along the line are often recorded. This method is necessary to confirm complete bidirectional block but repeating it frequently during the ablation process is relatively cumbersome. Specifically, it does not provide real-time information on transisthmus conduction time during ongoing RF application. Moreover, trans isthmus conduction delay observed during CS pacing does not imply bidirectional block across the MI line (Figure 7). LAA pacing during ongoing RF application is useful,[19] however many centers use single-catheter technique for LA ablation procedures.
and MI ablation is performed during distal CS pacing. Thus, the preprocedural knowledge of
the range of PMCT values obtained from the patients with bidirectional conduction block
across MI could be useful.

Parameters Influencing Peri-Mitral Conduction Time

This study showed that LA size and AF type were significantly associated with PMCT
independently. The results seem quite logical. The impulse generated by pacing close to the
completely blocked isthmus travels to its opposite side along the perimital annular
circuit.[5.11] The time it takes for the impulse to arrive at the opposite end of the blocked
isthmus is directly related to the perimeter of the annulus and inversely related to the
conduction velocity of the impulse traveling along the perimital annulus. The LA size
determines the perimeter of mitral annulus, so the conduction time is higher in patients with
bigger LA. The structural and electrophysiological changes due to AF (atrial remodeling)
include shortening of the refractory period and conduction slowing.[20.21] Therefore the
conduction time in patients with persistent AF is longer than paroxysmal AF. Other clinical
and echocardiographic parameters were not found to influence PMCT after multivariate
analysis in this study.

Relationship between Index and Second procedure-related Peri-mitral Conduction Time
Because AF promotes atrial remodeling,[20.21] PMCT continues to rise in patients with recurrent AF following the index procedure. On the other hand, reverse anatomic remodeling of LA from successful AF abolition might be contributory to relatively shorter PMCT in patients without AF recurrence. A state of mutual balance between these factors could be the determinant of PMCT during the second procedure. In this study, wherein there was no significant difference in the LA size and use of amiodarone between the index and second procedures, there was a significant correlation between the PMCT values obtained at the index and the second procedures over the whole population. In each one of 75% patients, the difference between the PMCT values obtained at two separate procedures is less than 30ms.

**Estimation of Complete Block from Peri-mitral Conduction Delay**

Complete MI block was found to be universally absent when peri-mitral conduction delay was less than 130 ms. On the other hand, peri-mitral conduction delay value more than 173ms predicted MI block in 88% of patients. The cutoff value of peri-mitral conduction delay in lower score group was lower than that in higher score group. Conventional pacing and mapping techniques are necessary for final confirmation of MI conduction block because there was an overlap in the PMCT values between the two groups making a single peri-mitral conduction delay value insufficient for the conclusion of complete MI block, of its own. However, the preprocedural availability of such information should help to facilitate the
challenging task of MI linear ablation.

Clinical Implication

The results of the present study have potential clinical implications. First, target PMCT can be estimated before the MI ablation procedure from easily available pre-procedural parameters. Second, at the second procedure for MI ablation, target PMCT higher than that during the index procedure should not be expected in usual circumstances. Third, although several pacing maneuvers are necessary to confirm complete MI block, the value of peri-mitral conduction delay >173ms is shown to predict complete MI line block in 88% of patients. The availability of this information before the procedure may help us to know the right time when pacing maneuver should be performed to ensure the achievement of trans isthmus conduction block. This could potentially reduce the total procedural duration.

Limitations

This marker applies only to a specific lesion set which was undertaken uniformly in all the patients in the present study. However, this is the most popular lesion set for MI isthmus linear ablation in the LA. Since many patients required electrogram-based ablation before undertaking MI linear ablation, its impact on the trans isthmus conduction delay and the duration of MI linear ablation could not be eliminated from the analysis. Although it could
have been studied like the other parameters in the study for its influence on PMCT, in coherence with the objective of the study, we refrained from including the parameters other than those which were preprocedural.

Conclusions

LA size and AF type have a significant influence independently on the PMCT associated with complete MI block. These pre-procedural parameters can be used to predict the expected PMCT value during left atrial MI ablation. Although detailed mapping and pacing techniques are necessary for final confirmation of complete linear block, we believe that the information obtained from the peri-mitral conduction delay value has significant clinical utility during MI ablation procedures. Whereas delay >173ms predicts bidirectional block with 86% accuracy, delay < 130ms completely rules out the possibility of block across the MI.

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Conflict of Interest Disclosures: None
References:


14. Becker AE. Left atrial isthmus: anatomic aspects relevant for linear catheter ablation


Table 1. Patient Clinical Characteristics

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<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age (years)</td>
<td>58 ± 10</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>243/47</td>
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<td>AF type (n)</td>
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<tr>
<td>Paroxysmal</td>
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<tr>
<td>Persistent</td>
<td>75 (25.9%)</td>
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<tr>
<td>Long-standing persistent</td>
<td>128 (44.1%)</td>
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<tr>
<td>Structural heart disease (n)</td>
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<tr>
<td>Ischemic heart disease</td>
<td>21 (7.2%)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>21 (7.2%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>28 (9.7%)</td>
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<tr>
<td>Duration of AF (months)</td>
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<tr>
<td>Ineffective AADs (n)</td>
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<td>Amiodarone (n)</td>
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<tr>
<td>LAD (mm)</td>
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<tr>
<td>LVEF (%)</td>
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</table>

AADs = antiarrhythmic drugs; LAD = left atrial diameter; LVEF = left ventricular ejection fraction.

Figure Legends:

Figure 1. Demonstration of bidirectional MI block. A. RF catheter is positioned on the MI line. During pacing from proximal CS (CS3-4), the delay from the pacing artifact to the atrial potential on the RF catheter is 168 ms. B. Changing the pacing site to distal CS (CS1-2) results in a longer peri-mitral activation time (178 ms, B). C. Pacing performed from LAA results in proximal-to-distal activation in the CS. Bidirectional conduction block was
confirmed by these findings.

**Figure 2.** The conduction delay of each part (A. low, B. middle, C. high) on the mitral isthmus line during CS3-4 pacing. Note the ratio atrial and ventricular potential.

**Figure 3.** Anteroposterior view with a schematic representation of the mitral annulus (MA), right and left PV, LAA, and MI line (pair of broken white lines). Decapolar catheter inserted into the CS, and ablation catheter placed on the MI line. The PMCT (circular arrow) was evaluated by pacing septal to the line of block (pacing sign) and recording the second late potential (red arrow) on the line of block.

**Figure 4.** Bland and Altman plot for the evaluation of stability of PMCT. The mean PMCT did not change significantly in the population. Individually, the difference in PMCT between 1st procedure and 2nd procedure was less than 30 ms in about 75% patients.

**Figure 5.** Peri-mitral conduction delay in patients with and without complete block in each group based on the cumulative score. Mean PMCT and the 95% confidence interval (CI) limits are also shown.

**Figure 6.** The receiver-operator characteristic (ROC) curve analysis of the peri-mitral
conduction delay and achievement of MI block. The optimal cut-off points (red arrows), area under curve (AUC) and the 95% confidence interval are also shown.

Figure 7. Example of real time monitoring of conduction delay on the MI line during CS distal pacing. A. The conduction delay was absent on the line during CS distal pacing before ablation. B. The delay of 122ms was achieved by RF application; however, LAA pacing showed that conduction block was not achieved. C. The delay prolonged suddenly from 122ms to 180ms during RF application, and bidirectional conduction block was confirmed by LAA pacing following this application (D). Note that we can record the local conduction delay on the MI line continuously during ongoing linear ablation. E. Example of real time monitoring of conduction delay on the line during distal CS pacing. The conduction got delayed suddenly from 64ms to 134ms (red arrows) during RF application but then after several beats, it resumed (blue arrow) at the same pace as before.
Peri-Mitral Conduction Time (PMCT)

PV: pulmonary vein
LAA: left atrial appendage
MA: mitral annulus
The ROC curves for models with different scores are shown in the image. The area under the curve (AUC) for each score is as follows:

<table>
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<th>Area</th>
<th>Standard Error</th>
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<tr>
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<td>0.0351</td>
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