Increased Carotid Artery Intimal-Medial Thickness in Asymptomatic Older Subjects With Exercise-Induced Myocardial Ischemia

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Background—Previous studies have shown an association between symptomatic coronary artery disease (CAD) and increased intimal-medial thickness of the common carotid artery (CCA IMT), a purported index of atherosclerosis. This study determines whether CCA IMT is increased in asymptomatic older subjects with an ischemic ST-segment response to treadmill exercise.

Methods and Results—CCA IMT was measured by B-mode ultrasound in community-dwelling volunteers from the Baltimore Longitudinal Study of Aging, including 397 healthy subjects (age, 58.5±15.8 years) with normal ECG responses to maximum treadmill exercise, 72 asymptomatic subjects (age, 66.1±13.4 years) with exercise-induced horizontal or downsloping ST-segment depression ≥1 mm, and 38 subjects (age, 77.4±7.8 years) with clinically manifest CAD as diagnosed by medical history and resting ECG. Forty-three subjects with abnormal exercise ECGs also underwent exercise thallium scintigraphy. Exercise-induced ST-segment depression was associated with increased IMT (P<0.0001) independent of age and manifest CAD. After adjustment for age, IMT values progressively increased from healthy subjects to asymptomatic subjects with positive exercise ECG alone to those with concordant positive ECG and thallium scintigraphic findings who had virtually identical IMT to subjects with manifest CAD. Each 0.1-mm increase in IMT was associated with a 1.91-fold (95% CI, 1.46 to 2.50; P<0.0001) increased risk for concordant positive exercise tests or manifest CAD, independent of other significant predictors of CAD.

Conclusions—CCA IMT is increased in older subjects with asymptomatic myocardial ischemia as evidenced by exercise ECG alone or in combination with thallium scan. Carotid ultrasound may help to identify asymptomatic individuals with CAD. (Circulation. 1998;98:1504-1509.)

Key Words: coronary disease • carotid arteries • ultrasonics • exercise • risk factors

Asymptomatic coronary artery disease (CAD) is prevalent in the general population,1,2 and individuals with CAD are at greater risk than those who are disease free to progress to symptomatic CAD and cardiac death.1,2 Early identification and preventive treatment for asymptomatic CAD can potentially lower the risk for subsequent symptomatic CAD. The exercise ECG remains the most commonly used screening method to detect asymptomatic myocardial ischemia. Numerous studies have shown that an ischemic ST-segment response to exercise is a risk factor for future coronary events in apparently healthy adults.1-3 Moreover, the predictive value of exercise ECG is improved by a combined use of thallium scintigraphy.1,4

B-mode ultrasonography allows for the noninvasive observation of age-associated normative and pathological changes in the carotid arterial structure, including wall thickening5,6 and lumen enlargement.7,8 An association has been demonstrated between increased intimal-medial thickness (IMT) of the common carotid artery (CCA) and conventional atherosclerotic risk factors, including hypertension,9,10 diabetes,11,12 hyperlipidemia,13,14 and cigarette smoking.15,16 Furthermore, several studies have shown a significant association of CCA IMT not only with cerebrovascular disease but also with clinical CAD.6,17

Despite the association between increased CCA IMT and clinically manifest CAD, it is unclear whether increased IMT also occurs in subjects with subclinical CAD. We hypothesized that CCA IMT would be increased in asymptomatic subjects with exercise-induced myocardial ischemia. To examine this hypothesis, we performed B-mode carotid ultrasonography and maximal treadmill exercise ECG testing in a sample of apparently healthy community-dwelling volunteers. To amplify the hypothesis, we performed exercise thallium scintigraphy in those asymptomatic subjects with
The aim of this study was therefore to determine (1) whether CCA IMT is increased in asymptomatic subjects with an exercise-induced ischemic ST-segment depression and (2) whether among these asymptomatic individuals with ischemic exercise ECG, CCA IMT is larger in the subset with an abnormal exercise thallium scan than in those with a negative scan.

Methods

Subjects

Subjects were recruited from the Baltimore Longitudinal Study of Aging (BLSA). The BLSA is made up of community-dwelling, predominantly white, college-educated volunteers who are studied approximately every 2 years with 2.5 days of extensive medical, physiological, and psychological examinations. The BLSA was started in 1958 and has recruited participants continuously since that time.

Treadmill exercise testing has been used in the BLSA since 1969 to screen for silent CAD. In 1977, exercise thallium scintigraphy was incorporated into the BLSA and has been offered to subjects >40 years at 8- to 10-year intervals. Carotid and cerebral artery ultrasound examinations were added to the BLSA evaluation in 1994. Inclusion criteria for the current study were (1) achievement of ≥85% of age-predicted maximal heart rate on treadmill exercise sound examinations were added to the BLSA evaluation in 1994. Inclusion criteria for the current study were (1) achievement of ≥85% of age-predicted maximal heart rate on treadmill exercise testing in subjects without clinical CAD and (2) no stenosis ≥50% or localized plaque in the CCA proximal to the bifurcation as detected by duplex carotid ultrasonography. Both exercise testing and carotid ultrasound protocols were approved by the Johns Hopkins Bayview Institutional Review Board, and informed consent was obtained from all subjects.

Carotid Ultrasonography

High-resolution B-mode carotid ultrasonography was performed by use of a linear-array 5- to 10-MHz transducer (Ultramark 9 HDI, Advanced Technology Laboratories, Inc). The subject lay in the supine position in a dark, quiet room. Blood pressure (BP) was measured at 5-minute intervals during the measurements (Critikon 1846SX/P, version 085, Dinamap). The stabilized BP after 15 minutes from the onset of testing was used for subsequent analyses. The right CCA was examined with the head tilted slightly upward in the midline position. The transducer was manipulated so that the near and far walls of the CCA were parallel to the transducer footprint and the lumen diameter was maximized in the longitudinal plane. A region of 1.5 cm parallel to the carotid bifurcation was identified, and the IMT of the far wall was evaluated as the distance between the luminal-intimal interface and the medial-adventitial interface. IMT was measured on the frozen frame of a suitable longitudinal image with the image magnified to achieve a higher resolution of detail. The IMT measurement was obtained from 5 contiguous sites at ~1-mm intervals, and the average of the 5 measurements was used for analyses. All the measurements were performed by a single sonographer (M.K.K.) who was unaware of the findings of the exercise ECG or thallium scintigraphy. Intraoperator correlation between repeated IMT measurements from 10 subjects was 0.96 (P<0.001), with similar averages for the 2 sets of readings (0.47±0.13 versus 0.45±0.12 mm, P=NS).

Maximal Treadmill Exercise ECG

Maximal treadmill exercise testing was conducted according to a modified Balke protocol in which the treadmill speed was held constant (usually 3.5 mph for men and 3.0 mph for women) and the elevation was raised 3% every 2 minutes, starting from horizontal, until exhaustion. A 12-lead ECG was recorded during the final 30 seconds of each 2-minute stage and every 2 minutes for at least 6 minutes of recovery. The exercise ECG was interpreted according to Minnesota Code criteria. A positive ECG response for ischemia was defined as horizontal or downsloping ST-segment depression ≥1 mm. Lesser degrees of ST-segment depression were interpreted as negative.

Exercise Thallium Scintigraphy

The test was performed in the Johns Hopkins Hospital Nuclear Cardiology Laboratory with the identical maximal treadmill exercise protocol. 201 Tl (3 mCi IV) was injected 1 minute before anticipated exercise cessation. After 5 to 10 minutes of postexercise ECG monitoring, myocardial scanning was begun. Tomographic imaging was performed with a Technicare Omega 500 rotating, large-field-of-view camera interfaced to a Technicare 560 computer. Delayed imaging was performed 3 hours later without reinjection of thallium. Image interpretation was performed visually by an experienced nuclear cardiologist (L.C.B.) who was unaware of the clinical history, carotid ultrasound results, and exercise ECG findings. Results were coded as positive or negative for reversible ischemia. A positive thallium tomogram was defined by a segmental perfusion defect on the immediate postexercise images in at least 2 contiguous tomographic slices and 2 image orientations, with definite improvement or normalization on the delayed images.

Assessment of CAD

On the basis of medical history, resting ECG, maximal treadmill exercise ECG, and clinical symptomatology, subjects were classified into 3 CAD categories: no CAD, possible CAD, and definite CAD. The no CAD group comprised subjects with no history of angina pectoris or myocardial infarction and without pathological Q waves or exercise-induced horizontal or downsloping ST-segment depression ≥1 mm. Possible CAD was defined by asymptomatic ischemic ST-segment depression ≥1 mm but without clinical symptoms or resting ECG evidence of myocardial infarction. The results of thallium scintigraphy were used to further stratify possible CAD subjects into 2 subsets: group 1, possible CAD-1, with a positive exercise ECG but negative thallium scan, and group 2, possible CAD-2, with concordant positive exercise ECG and thallium scan. We analyzed only those subjects who had undergone thallium scintigraphy within 5 years of the carotid examination (mean, 2.0±1.9 years). Definite CAD was diagnosed by a history of acute myocardial infarction, silent infarction documented by significant Q waves on ECG (Minnesota Code 1:1 or 1:2), or unequivocal angina pectoris as defined by the Rose questionnaire.

Statistical Analysis

Intergroup differences in age, coronary risk factors, and CCA IMT were examined by 1-way ANOVA followed by Bonferroni’s multiple-comparisons test. The risk factors considered in this study were male sex, body mass index (BMI), systolic BP, diastolic BP, fasting plasma glucose (FPG), serum total cholesterol (TChol), TChol/HDL cholesterol ratio (TChol/HDL), LDL cholesterol (LDL-C), and smoking. Smoking status was categorically defined on the basis of self-reports, with a smoker defined by current or past smoking ≥10 cigarettes per day. The association of IMT with coronary risk factors and CAD status was evaluated by multiple regression analyses. The association of IMT with thallium scintigraphic findings was assessed by the differences in age-adjusted mean IMT. The ability of IMT to predict CAD was examined by logistic regression analysis. Data are presented as mean±SD unless otherwise specified, and a 2-tailed P<0.05 was considered statistically significant. All analyses were performed by use of SPSS for Windows 6.1.

Results

Baseline Characteristics Stratified by CAD Status

CCA IMT and CAD status were evaluated in 507 subjects, including 261 men (age, 64.0±15.7 years; range, 25 to 95 years) and 246 women (age, 57.8±15.6 years; range, 27 to 93 years). Baseline characteristics for the no CAD, possible
Increased CCA IMT and Asymptomatic CAD

### TABLE 1. Baseline Characteristics by CAD Status

<table>
<thead>
<tr>
<th></th>
<th>No CAD (n=397)</th>
<th>Possible CAD (n=72)</th>
<th>Definite CAD (n=38)</th>
<th>P by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.5±15.8</td>
<td>66.1±13.4</td>
<td>77.4±7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>46.9</td>
<td>62.5†</td>
<td>78.9†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1±4.3</td>
<td>26.9±4.1</td>
<td>26.2±3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>120.2±15.6</td>
<td>128.0±18.7†</td>
<td>130.7±17.0†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>68.9±9.8</td>
<td>69.7±9.0</td>
<td>70.2±15.9</td>
<td>NS</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>94.7±16.7</td>
<td>100.3±25.7</td>
<td>109.6±37.7†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TChol, mg/dL</td>
<td>177.6±34.4</td>
<td>179.2±33.0</td>
<td>172.4±35.2</td>
<td>NS</td>
</tr>
<tr>
<td>TChol/HDL</td>
<td>4.0±1.3</td>
<td>4.1±1.3</td>
<td>4.4±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>106.8±31.1</td>
<td>109.9±28.7</td>
<td>105.9±28.3</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>26.3</td>
<td>29.2</td>
<td>28.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

No CAD indicates asymptomatic with negative exercise ECG; possible CAD, asymptomatic with positive exercise ECG; and definite CAD, angina pectoris and/or history or resting ECG evidence of myocardial infarction. For continuous variables, values indicate mean±SD.

*All groups differ at P<0.05; †P<0.05 vs no CAD.

### Figure 1. CCA IMT by CAD status defined by exercise ECG and clinical manifestations. Group definitions are as follows: no CAD, subset with negative clinical history and normal exercise ECG; possible CAD, subset with negative clinical history but ischemic exercise ECG; and definite CAD, subset with angina pectoris, a history of myocardial infarction, and/or pathological Q waves in resting ECG. Error bars indicate SD.

### Association of CCA IMT With Coronary Risk Factors and CAD Status

By univariate regression analysis, CCA IMT increased with age, systolic BP, diastolic BP, FPG, and each lipid measure but not with BMI (Table 2). A quadratic term was also examined for each variable, but the explicable variance was similar to that obtained by linear regression. IMT also was larger in smokers than in nonsmokers (0.59±0.15 versus 0.55±0.16 mm, P<0.01).

To further clarify the significant associates of CCA IMT, IMT was regressed on age, sex, other coronary risk factors, and their respective medications (Table 3). By backward elimination, medications, smoking, TChol, FPG, LDL-C, diastolic BP, and BMI did not significantly contribute to the models and are not shown in the table. Larger CCA IMT was associated with older age (β=0.59, P<0.0001), male sex (β=0.08, P<0.05), higher systolic BP (β=0.15, P<0.0001), and higher TChol/HDL (β=0.08, P<0.05) (Table 3, model 1). When CAD status was added to the original model, age and sex were significant independent variables (Table 3, model 2).

### TABLE 2. Univariate Regressions of Coronary Risk Factors on CCA IMT

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>Intercept, mm</th>
<th>Slope (×10⁻³)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.68</td>
<td>0.16</td>
<td>6.5 mm/yr</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.05</td>
<td>0.51</td>
<td>1.6 mm/(kg·m⁻²)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.42</td>
<td>0.08</td>
<td>3.9 mm/mm Hg</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.13</td>
<td>0.42</td>
<td>2.0 mm/mm Hg</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FPG</td>
<td>0.19</td>
<td>0.42</td>
<td>1.4 mm/(mg·dL⁻¹)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TChol</td>
<td>0.09</td>
<td>0.48</td>
<td>0.4 mm/(mg·dL⁻¹)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TChol/HDL</td>
<td>0.17</td>
<td>0.48</td>
<td>19.9 mm/U</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.14</td>
<td>0.48</td>
<td>0.7 mm/(mg·dL⁻¹)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
TABLE 3. Multiple Regression of CCA IMT on Age, Coronary Risk Factors, and CAD Status

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$0.59^*$</td>
<td>$0.53^*$</td>
</tr>
<tr>
<td>Possible CAD</td>
<td>$§$</td>
<td>$0.14^*$</td>
</tr>
<tr>
<td>Definite CAD</td>
<td>$§$</td>
<td>$0.20^*$</td>
</tr>
<tr>
<td>Sex (men=$1$)</td>
<td>$0.08^†$</td>
<td>$</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>$0.15^*$</td>
<td>$0.14^*$</td>
</tr>
<tr>
<td>TChol/HDL</td>
<td>$0.08^†$</td>
<td>$0.09^‡$</td>
</tr>
<tr>
<td>(Model $r^2$)</td>
<td>$(0.50)$</td>
<td>$(0.55)$</td>
</tr>
</tbody>
</table>

Possible and definite CAD are as defined in Table 1. Numbers represent standardized regression coefficients. This table shows significant regressors of IMT determined by backward elimination from the model including age, sex, other coronary risk factors, and their respective medications. *$P<0.0001$; †$P<0.05$; ‡$P<0.01$; §Not considered for the model; ||Not significant and excluded from the model.

had the strongest association with IMT ($β=0.53, P<0.0001$), followed by definite CAD ($β=0.20, P<0.0001$), possible CAD ($β=0.14, P<0.0001$), systolic BP ($β=0.14, P<0.0001$), and TChol/HDL ($β=0.09, P<0.01$) (Table 3, model 2), with overall $r^2$ improving from 0.50 to 0.55. Sex and CAD status had no interaction with age or other continuous variables. Furthermore, no sex differences were found in predicting IMT with CAD status included (Table 3, model 2).

CCA IMT in Possible CAD Subjects Stratified by Thallium Scintigraphic Findings

To further clarify the relationship between CCA IMT and CAD status, we further stratified possible CAD subjects by exercise thallium scintigraphic findings. Sixty percent of possible CAD subjects (43 of 72) underwent thallium scans. Coronary risk factors and CCA IMT were similar between subjects with thallium scan results and those without them (data not shown).

Among the 43 subjects undergoing thallium scanning, 30 had negative scans and were classified as possible CAD-1 (positive exercise ECG alone), and 13 had positive scans and were classified as possible CAD-2 (concordant positive exercise ECG and thallium results). Only 2 women were possible CAD-2 subjects, making sex comparisons impossible. A graded increase in IMT was observed from subjects with no CAD ($0.52±0.14$ mm) to those classified as possible CAD-1 ($0.61±0.12$ mm) to possible CAD-2 ($0.74±0.10$ mm) (Figure 2). These group differences in IMT remained significant after adjustment for age (Table 4). Of note, the IMT in possible CAD-2 subjects was virtually identical to that in the definite CAD group.

Prediction of CAD by CCA IMT

To examine the contribution of CCA IMT in predicting CAD, we performed a logistic regression analysis with both possible CAD-2 and definite CAD as end points. In this analysis, the univariate risk for CAD increased by 2.39-fold ($χ^2=84.0, P<0.0001$; 95% CI 1.92 to 2.96) for each 0.1-mm increase in IMT compared with no CAD subjects. Furthermore, IMT was an independent predictor for CAD when controlling for age, coronary risk factors, and their respective medications. With backward elimination, each 0.1-mm-greater IMT independently increased the risk for CAD by 1.91 (1.46 to 2.50) in the most parsimonious model (Table 5). No interaction was observed among these variables.

Discussion

The present study demonstrates a significant independent association between increased IMT and asymptomatic CAD as evidenced by ischemic ST-segment depression on the exercise ECG. Furthermore, there was a graded increase in IMT from CAD-free subjects to those with only a positive exercise ECG to those with concordant positive exercise ECG and thallium scans. These last individuals had an IMT that was essentially equal to that in patients with clinically manifest CAD. By logistic regression analysis, CCA IMT proved to be an independent predictor for manifest CAD and concurrent positive exercise test results.

A positive association between carotid and coronary atherosclerosis is well recognized. The increase in IMT from no CAD to possible CAD to definite CAD is consistent with the concept that coronary atherosclerosis is a continuum from normal through an asymptomatic stage to overt CAD. Furthermore, the asymptomatic CAD was independently associated with increased CCA IMT (Table 3), suggesting that not only subjects with clinically manifest CAD but also those with evidence for asymptomatic CAD have increased IMT.

To further stratify the likelihood of asymptomatic CAD in the possible CAD group, we subdivided this group on the basis of their exercise thallium scintigraphic findings. A prior study from our laboratory demonstrated that concordant positive exercise ECG and thallium test results identify a...
subset of asymptomatic subjects at twice the risk for CAD events as those with a positive ECG alone, with \( \approx 50\% \) of these “double positives” developing clinical endpoints over a mean follow-up of 4.6 years. In the present study, after adjustment for age, a graded increase in IMT was observed from CAD-free subjects to those with only a positive exercise ECG to those with concordant positive exercise ECG and thallium tests (Table 4). Thus, CCA IMT appears to increase in parallel with the increase in risk for myocardial ischemia as assessed by these noninvasive tests. It is noteworthy that this latter subset with asymptomatic ischemia on both exercise ECG and thallium scan demonstrated a mean IMT virtually identical to that in the group with manifest CAD (Figure 2).

If CCA IMT increases in parallel with the likelihood of CAD, this association may be useful in identifying asymptomatic subjects with significant CAD. We have considered manifest CAD and asymptomatic CAD (confirmed by the concordant positive exercise ECG and thallium results) as essentially the same clinical entity on the basis of our prior observations. On univariate analysis, the likelihood for CAD increased by 2.39-fold for each 0.1-mm increase in IMT. Furthermore, IMT was an independent predictor for CAD, increasing the risk by 1.91-fold for each 0.1 mm when controlling for the significant effects of age, hypertensive, and hyperlipidemic medications (Table 5).

The increase in IMT with the likelihood of CAD appears to be similar for both women and men. Men have thicker IMT than women at all levels of CAD status, but the degree of thickening going from no CAD to possible CAD-1 to definite CAD was similar by sex. In the multiple regression analysis (Table 3, model 2), sex did not add to the prediction of IMT when stage of CAD was included. Also, sex did not affect the prediction of CAD by IMT (Table 3). However, with only 8 women with definite CAD and 2 women with possible CAD-2, our power to detect sex differences was limited in Table 3.

Although the overlap of CCA IMT between non-CAD and CAD subjects (Figure 1) precludes the use of IMT alone as a diagnostic marker for CAD, our observation suggests the utility of further screening for CAD in subjects with increased IMT, even if asymptomatic. As suggested in Table 5, such screening would likely be most useful in older subjects with hypertension or hyperlipidemia. The threshold for exercise screening will depend on factors such as the pretest likelihood of CAD, the age and lifestyle of the individual, and the cost of exercise testing. Although aggressive medical or surgical treatment of silent myocardial ischemia has proven beneficial in patients with symptomatic CAD, the utility of such therapy in totally asymptomatic subjects remains unclear.

In addition, regression or slowed progression of IMT has been reported in subjects on lipid-lowering therapy. If IMT changes in parallel with the progression of CAD, serial measurement of IMT may serve as a noninvasive marker for the efficacy of risk factor modification with antihypertensive and lipid-lowering therapy.

Prior studies have shown independent effects of age and conventional coronary risk factors on CCA IMT. In the present study, IMT increased with age, systolic BP, diastolic BP, and each lipid measure (Table 2) and was larger in men and in smokers. However, independent associations were confirmed only with age, systolic BP, male sex, and TChol/HDL (Table 3, model 1). Age, systolic BP, and TChol/HDL remained significant predictors of IMT even after CAD status was included in the model (Table 3, model 2), suggesting their strong atherogenic effects. The relatively low mean levels of FPG, TChol, and LDL-C in the BLSA subjects, as well as the low prevalence of smokers, probably account for their weak associations with IMT.

One limitation of the present study was a reliance on exercise ECG and thallium scintigraphy to stratify the likelihood of CAD. Although the ability of these exercise testing modalities to identify asymptomatic individuals at higher risk for a future coronary event has been shown in the BLSA and in other studies, such noninvasive stratification is imperfect.

In summary, this study demonstrates a significant association between asymptomatic exercise-induced myocardial ischemia and increased CCA IMT, similar to that seen in patients with manifest CAD. Although the primary purpose of carotid ultrasonography is not the detection of CAD, determination of IMT may help to identify asymptomatic individ-
uals with a high likelihood for CAD and provide a noninvasive window for monitoring the efficacy of risk factor modification in these subjects.

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References
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