Journal of Cardiovascular Magnetic Resonance (2007) **9,** 771–776

ISSN: 1097-6647 print / 1532-429X online
DOI: 10.1080/10976640701544746

The Reliability of High Resolution MRI in the Measurement of Early Stage Carotid Wall Thickening

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ABSTRACT

Purpose: **To study the repeatability of common carotid mean wall thickness (MWT) measured with high resolution MRI, in comparison with intima media thickness (IMT) assessed by ultrasound and to investigate the relative capabilities of these two modalities. *Materials and methods:* Ten healthy volunteers and 10 subjects with carotid artery atherosclerosis were imaged with both high resolution MRI and US. Measurement of both MWT and IMT was performed by three blinded observers. Intra- and inter-observer repeatability was calculated and a Bland-Altman plot used to compare IMT and MWT. Circumferential variation in arterial wall thickness was also evaluated. *Results:* Intra- and inter-observer repeatability were comparable between IMT and MWT. The Bland-Altman plot showed a difference between IMT and MWT in controls with a trend towards equivalence in atherosclerotic patients. Analysis of circumferential variation in wall thickness by MRI identified greater focal thickening in patients compared with controls ($p < 0.001$), which was not evident with ultrasound ($p = 0.98$). *Conclusion:* MRI and ultrasound have similar repeatability for the assessment of carotid wall thickness. There are differences between MWT and IMT, potentially due to the inclusion of the adventitia by MRI which, in addition to better detection of focal thickening, may provide a more complete estimation of early stage atherosclerosis.**

INTRODUCTION

Cardiovascular disease is a major cause of mortality and morbidity in industrialized countries. While clinical cardiovascular events do not normally manifest until the fifth decade of life, atherosclerosis, the underlying chronic inflammatory disease, is a life long process. It is characterized by progressive changes in arterial wall structure and composition which are influenced by cardiovascular risk factors such as hypercholesterolemia, hypertension, and diabetes. There is a need for an integrative marker of atherosclerosis in order to focus prevention in high risk subjects. A preclinical marker of atherosclerotic progression is artery wall thickening. Non-invasive assessment of carotid arterial wall thickness is therefore frequently used to assess preclinical cardiovascular disease. This is commonly performed by measuring the intima-media thickness (IMT) of the carotid artery using high-resolution ultrasound (US) (1, 2). It has been demonstrated that not only are increases in IMT strongly associated with cardiovascular risk factors but, furthermore, that IMT predicts the future risk of clinical cardiovascular events (3, 4). Consequently, IMT is often used in clinical trials and cohort studies as a surrogate marker of cardiovascular disease.

High resolution MRI is a new tool to analyze carotid plaques (5–7). Specifically, it allows good plaque delineation and in vivo plaque composition characterization. The great majority of MR studies of carotid atherosclerosis have been directed at relatively advanced disease states with diameter narrowing typically greater than 50% where atheroma is several millimeters thick. There have been few investigations of the use of MRI for measuring thickening of the wall of the common carotid artery

Received 10 January 2007; accepted 11 June 2007.
Keywords: Intima Media Thickness, High Resolution MRI, Adventitia, Atherosclerosis
Michael R. Skilton was supported by the Fondation pour la Recherche Médicale.
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where early stage atherosclerosis manifests as wall thickening that is of the order of 0.5 mm, which is close to the spatial resolution of the MR acquisition. In this application, it is essential to determine both the correlation of MR measurements with the established standard, IMT, and also the reproducibility and robustness of MR measurement of MWT, as determined by an inter-reader analysis.

The aim of this study is, therefore, to assess the accuracy of high resolution MRI in evaluation of arterial thickening and to compare this technique with IMT assessed by high resolution US. We specifically focused on the repeatability of the two techniques and compared the results between a population of healthy volunteers and subjects with documented carotid artery atherosclerosis.

MATERIALS AND METHODS

Population

Informed consent was obtained from all participants. The study was performed in compliance with the requirements of our institutional review board. Ten healthy volunteers and 10 atherosclerotic patients were involved in this study. The healthy volunteers were 4 males and 6 females, aged from 25 to 47 years (mean age = 30.7 years). The atherosclerotic patients were 3 males and 7 females aged from 34 to 74 (mean age = 62.4 years). The cardiovascular risk factor (CVRF) analysis found that 7 patients presented with diabetes, 8 with hyperlipidemia, 6 with hypertension, 3 with tobacco use, 6 with obesity, and 5 with familial history of atherosclerosis. The inclusion criterion for the atherosclerotic patients was the presence of a carotid plaque measuring at least 1.5 mm (8) of the internal carotid artery as assessed by US. No other criterion, including clinical characteristics, was used to select these subjects.

Healthy volunteers were CVRF free (tobacco use, hypercholesterolemia, diabetes, hypertension, or particular familial history) as assessed by oral questionnaire. The MRI and US scans were carried out on the same day for the atherosclerotic patients and within a week of each other for the healthy volunteers. The hardware available for the MR portion of this study was a single radiofrequency coil, which only permitted evaluation of the extracranial carotid arteries on one side of the neck. Because of this, all US and MRI studies were conducted on one side only; for normals one side, either the right or left, was chosen at random, and for patients the side of the carotid artery with known atherosclerotic disease was chosen. In case of bilateral stenosis, the most stenotic artery was used for analysis.

US

US examination was performed by an experienced operator with a 7.5–10 MHz US transducer (Antares, Siemens, Erlangen, Germany). The side for examination was chosen as described above. The choice of US to include patient insure to have sufficiently echogenic patients as ultrasound is taken the as a "gold standard" technique in our study. The subjects were examined in the supine position with the neck extended and rotated 45° to the contralateral side. The transducer was centered on the common carotid artery, 2 cm proximal to the carotid bifurcation in the longitudinal plane. Images were recorded through the entire cardiac cycle and one image was selected by the operator at the diastolic phase and stored in DICOM format on the hard drive.

On the selected image, the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall was measured at 4 separate locations within a 1 cm range, centered 2 cm below the carotid bifurcation. The IMT was defined as the mean value of those 4 measurements. The images from the normal subjects and the patient group were randomized, and all observers were blinded to subject identity and group. Three experienced observers measured each image twice, and an average was taken of these two measures.

MRI

MRI examinations were conducted using a 1.5T system (Intera, Philips Medical Systems, Best, The Netherlands) using a surface coil (diameter = 47 mm) positioned on top of the mandibular angle. Scout bright blood images were first acquired in the axial plane covering 12 × 3 mm thick slices using a standard 2D time of flight sequence. The longitudinal course of the vessels was then determined using 5 × 3 mm parasagittal bright blood images, positioned on the scout axial images using a three-point plane prescription to include the CCA, ICA and ECA. T2 weighted MRI images were obtained using a 2D turbo spin echo sequence preceded by a black-blood double inversion recovery preparation. Fat saturation (FATSAT) was added to the sequence in order to better delineate the vessel wall by removing the signal of surrounding fat tissues. The sequence parameters were as follow: TR = 2 or 3 cardiac cycles (depending on the heart rate, TR ranged from 1650 to 2300 ms), TE = 23 ms, flip angle = 90°, field of view = 160 mm, matrix = 256 × 256, slice thickness = 2 mm, image resolution = 0.6 × 0.6 × 2 mm. Cardiac triggering was used, and images were obtained during the diastolic phase. A volume consisting of six slices without a slice gap was acquired perpendicular to the axis of the common carotid artery. The center of the volume was positioned 2 cm below the carotid bifurcation which was previously located with a multislice axial and parasagittal bright blood sequence. Each slice was acquired in 1 or 2 minutes depending on heart rate. Finally, to limit motion artifacts, the patient was asked to remain motionless and to swallow only between data acquisition.

The images were analyzed on a PC with the THERALYS Vascular Image Analysis software (Theralys, Lyon, France) (http://www.theralys.com/). Again, the images from the normal subjects and the patient group were randomized, and all observers were blinded to subject identity and group. All images were graded on a subjective 5 point scale of image quality: 1 = unacceptable; 2 = marginal; 3 = average; 4 = good; 5 = excellent. Images that received a mean score averaged over all readers of 2.5 or less were excluded from further analysis. For each slice, the inner and outer boundaries of the vessel wall were manually delineated by 3 experienced and independent observers.

Each observer was free to adjust the window/level parameter for each slice. The software automatically processed the vessel wall boundaries to obtain the wall thickness. For each slice, a wall central line was generated (ie, a closed contour equidistant from the inner and outer boundaries). Local wall thickness measures were then computed at regularly spaced locations along the central line (100 thickness measures per slice) by measuring the distance between the inner and outer boundaries in the direction perpendicular to the central line. The slice wall thickness measure was then obtained by averaging local wall thickness measures. In some cases (see below), slices were excluded from analysis because of image quality limitations. The final wall thickness (MWT) for each patient was the mean value of the measurements performed on all evaluated slices (maximum 6 per patient). Two measurements were made by each observer to assess intra-observer variability. These two measures for each observer were then averaged for other analyses.

Statistics

All statistical analyses were made using the Medcalc v 7.3.0.1 software package (Mariakerke, Belgium).

The inter-observer repeatability was estimated for each technique (US or MRI) and between the 3 observers using paired comparisons. For each pair of observers, the difference of the measurement (IMT or MWT) for each subject was calculated. The SD of these differences was then tabulated relative to the global mean value of the measurements. This final value is the inter-observer repeatability for each pair of observers. The intra-observer repeatability was similarly assessed for each observer, however, with the comparison being made between the two measurements performed by the same observer.

A Bland-Altman plot was used to compare US and MRI measures of carotid wall thickness (9). The mean value measured by the three observers was used for each subject.

Finally, we assessed the heterogeneity of the arterial wall thickness using both MRI and US. For MRI the circumferential variation of the arterial wall thickness was determined by calculating the standard deviation of the distance between the outer and inner contours relative to the MWT. We refer to this as the circumferential eccentricity. For US, longitudinal heterogeneity of the arterial wall was determined by calculating the standard deviation of the 4 measures of IMT for each vessel relative to the mean IMT. Those results were compared between patients and healthy controls using an unpaired t-test.

RESULTS

All patients were evaluated, and all 20 US images were deemed adequate for analysis. For MRI, a total of only 104 of the 120 potential slices were analyzed either because they did not meet the image quality acceptance criterion or because of failure to acquire the studies for the following reasons: for 4 subjects (1 patient and 3 volunteers), only 4 slices were acquired; 1 patient only had 1 slice that could be analyzed because of exam interruption (claustrophobia); and, for one patient (with 6 slices), 3 slices were rejected because of motion fuzziness. On examination of the imaging studies, all carotid segments visualized were considered to be free of plaque (ie, without focal thickening) both for MRI and US.

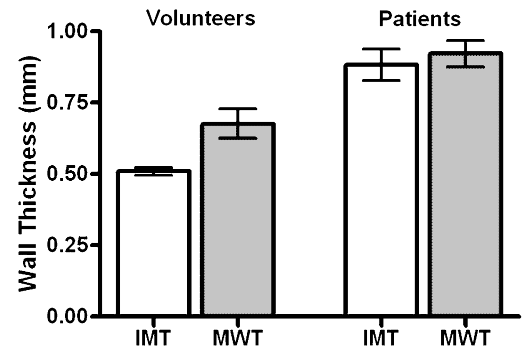

Figure 1. Mean value of intima media thickness (IMT measured by US) and mean wall thickness (MWT measured by MRI) for healthy volunteers and patients.

The mean IMT for patients was 0.88 ± 0.17 mm (range 0.51–1.11) and 0.51 ± 0.04 mm (range 0.44–0.59) for volunteers. The mean MWT for patient was 0.92 ± 0.14 mm (range 0.68–1.19) and 0.67 ± 0.05 mm (range 0.59–0.74) for volunteers (Fig. 1).

Mean intra-observer coefficient of repeatability was 8.4% for IMT (7.8, 8, and 9.4% respectively for each observer) and 10.5% for MWT measurement (8.2, 10.5, and 12.7%).

Mean inter-observer coefficient of repeatability was 8.2% (8.7, 8.3, and 7.7% respectively for each pair of observers) for IMT and 7.4% (6.2, 7.8, and 8.1%) for MRI measurement.

The comparison between IMT by B-mode US and MWT by MRI for the entire image set (Fig. 2) had a strong correlation with

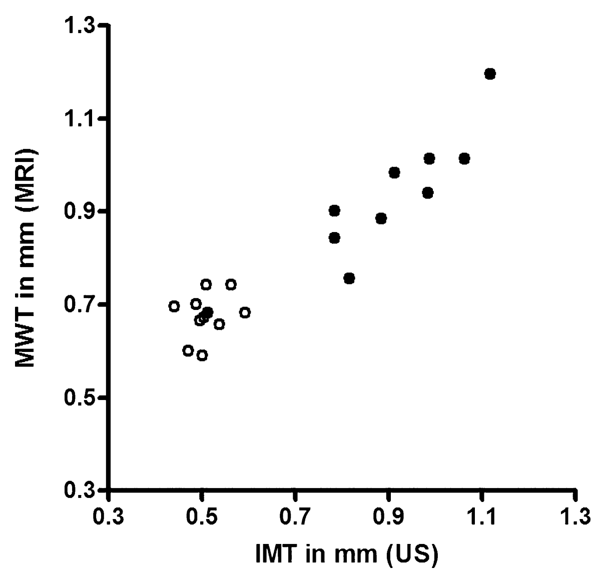

Figure 2. Scatter plot showing results of IMT measured by US and MWT measured by MRI. Open symbols represent healthy volunteers; solid symbols indicate atherosclerotic patients.

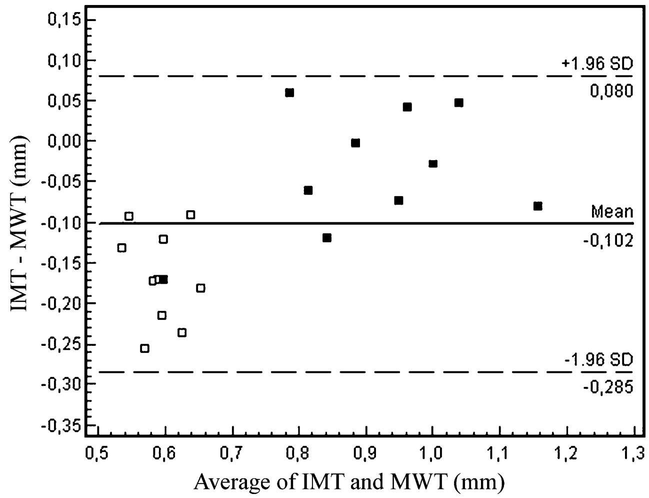

Figure 3. Bland-Altman plot representation of IMT and MWT. Lines show the mean ± 1.96 SD (95% confidence). Open symbols represent healthy volunteers; solid symbols indicate atherosclerotic patients.

a Pearson correlation coefficient equal to 0.93 ($p < 0.001$) and a r-square value of 0.88. The Bland-Altman analysis (Fig. 3) shows an upward bias in the MWT measurement and a trend to the reduction in this bias at higher values. A paired t-test performed on patients shows no statistical difference between MWT and IMT ($p = 0.15$) whereas a paired t-test on volunteers shows a strong statistical difference between the two techniques ($p < 0.0001$).

The mean value of the standard deviation of the wall thickness measurement with MRI relative to the MWT, to assess circumferential eccentricity of the arterial wall, was statistically different between patients and volunteers using an unpaired t-test: $20 \pm 3.6\%$ for patients and $15 \pm 1.7\%$ for volunteers ($p < 0.001$) (Fig. 4 and 5).

In contrast, the mean value of the standard deviation from the four measures of IMT in each patient relative to the mean IMT, to assess wall thickness heterogeneity, was not statistically different between patients and volunteers using an unpaired t-test: $9.5 \pm 4.6\%$ for patients and $9.6 \pm 2.7\%$ for volunteers ($p = 0.98$).

DISCUSSION

This study provides the first report of inter-reader reliability in the evaluation of thickening of the carotid wall for changes that are of the magnitude reported for early stage carotid disease. This study also demonstrates the capability of MRI to assess features of wall thickening that are not accessible in conventional transcutaneous US, namely abilities to determine non-uniformity in wall thickness around the circumference of vessel, and to assess adventitial thickening. Since atherosclerotic disease is known to present in many locations with substantial circumferential heterogeneity, a modality that is not limited to a single plane has advantages in providing a comprehensive evaluation of the disease process. Similarly, determination of adventitial thickening could also contribute to a more complete understanding of early stage carotid disease.

We compared the measurement repeatability attainable with MRI to that of US and obtained comparable, and indeed very good, inter-observer and intra-observer repeatability with both techniques. Our results in US were close to those obtained by others teams (10, 11). Studies by others, in the case of more advanced disease, indicate that there is also good inter-study reproducibility for MRI studies repeated within a short time

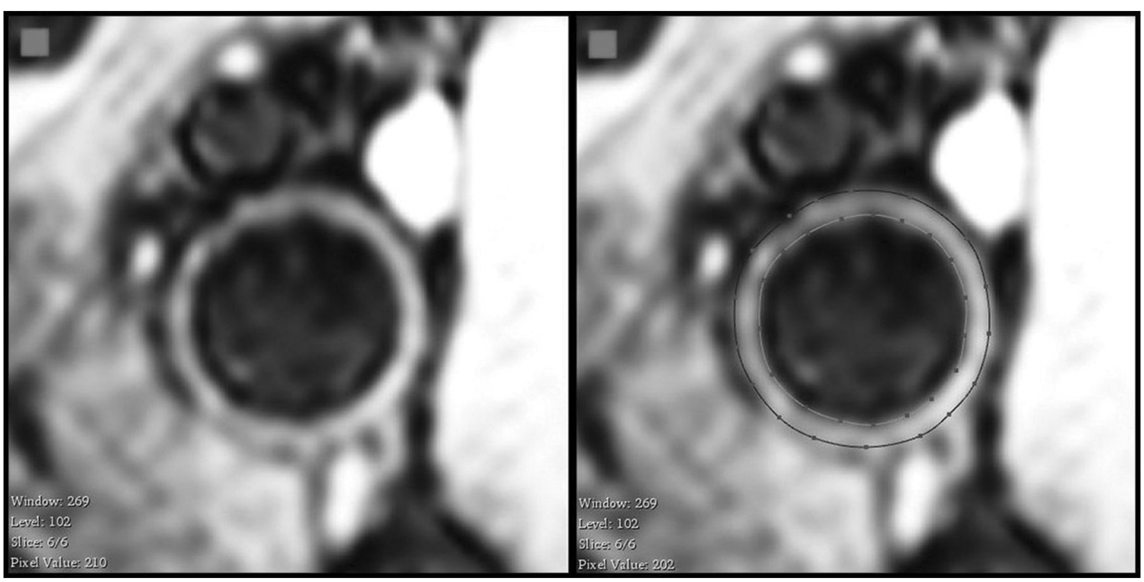

Figure 4. Region drawing on the MR images. An example of a healthy volunteer with a mean wall thickness of 0.65 mm and a low eccentricity (standard deviation: 0.028 mm, ie, eccentricity of 4.3% on this slice).

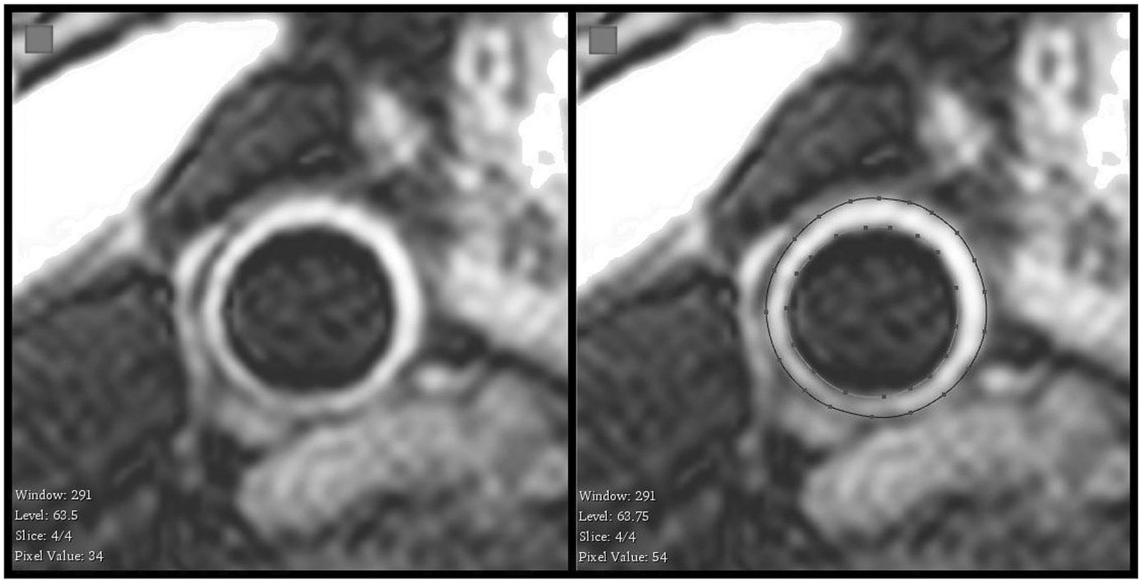

Figure 5. Example of region drawing on a patient. The mean wall thickness is 1.1 mm with important eccentricity (standard deviation: 0.133 mm ie eccentricity of 12% on this slice).

interval of each other in both asymptomatic subjects and patients with carotid atherosclerosis (12). This study demonstrates through an inter-reader reliability analysis that even in the case where changes in wall thickness are close to the resolution limit, MRI provides a reliable estimate of wall thickness.

In agreement with previous studies (13–15), our results show that measures of carotid wall thickness assessed using MRI and high-resolution US are strongly correlated. Analysis of the Bland-Altman representation shows a difference between MWT assessed by MRI and IMT assessed by US depending on the studied population. The measure of MWT is very close to that of IMT in subject with greater wall thickness (equivalently, the difference between IMT and MWT is close to zero) whereas, in controls, MWT is substantially greater than IMT. This trend towards parity with increasing wall thickness is supported by the findings of Underhill et al (14), who compared automatic and manual MRI carotid wall thickness measurement versus US measurement with similar methodology to our study. The origin of this difference remains unexplained but, because IMT excludes the adventitia from the measurement (8), we believe that the adventitia may play an important role in this relationship as there is some evidence (16) that modifications occur in the adventitia during the atherosclerotic process even at early stages of atherosclerosis.

As noted above, another potential advantage of MRI over ultrasound is the ability to obtain a more complete image of the artery via 3D imaging, thus increasing the probability of detecting areas of the arterial wall with pathological features. Indeed, using MRI, we found there was a greater eccentricity in arterial wall thickness in subjects with atherosclerosis as opposed to controls. Although transluminal US is an excellent method for looking at the vessel wall and has been used to demonstrate marked heterogeneity in the circumferential distribution of atheroma, it is highly invasive and not suited to a diagnostic evaluation. Transcutaneous US measures of IMT do not assess the lumen circumference, and circumferential heterogeneity was, therefore, not measured with US. MRI may, therefore, be particularly well-suited for monitoring atherosclerosis progression, or regression, during treatment.

The analysis of wall thickness in cardiac studies is commonly performed by partitioning the annulus into segments. Instead of performing a segmental analysis, we used a standard deviation measure to assess vessel eccentricity for two reasons. First, in the region of the common carotid artery that is usually evaluated for IMT, there is no report that one particular location around the circumference of the carotid artery is more prone to wall thickening than any other location. Second, the best method for performing a segmental analysis for the common carotid artery is currently unknown and was beyond the scope of this research. However, it is possible that the standard deviation was influenced by measurement error, resulting from inaccurate identification of the carotid wall boundaries due, for example, to partial volume effect. However, this is unlikely to be a major contributing factor as one would expect a greater influence of this error where there is a lower wall thickness. We observed the opposite - a markedly lower SD in control subjects as compared to that in atherosclerotic patients. This leads us to believe that this difference in the standard deviation represents a real change in wall eccentricity.

Finally, one potential advantage of MRI was not exploited in this study, namely the ability to perform studies of both carotid arteries in the same imaging acquisition. Such studies are possible using bilateral coils, but those coils are not yet provided by the major equipment vendors and were not available to this study.

In conclusion, while ultrasound is less expensive and is easily performed, there exist some potential advantages of MRI over ultrasound for the measurement of arterial wall thickness in early stage carotid disease. Indeed, MRI may provide additional information regarding the role of the adventitia and arterial wall eccentricity, while having similar repeatability to that of US. These features should be of particular interest in multi-center clinical trials as changes in eccentricity and total wall thickness, including the adventitia, may provide information beyond that attainable by carotid IMT alone.

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