In Vivo Quantification of Carotid Artery Wall Dimensions
3.0-Tesla MRI Versus B-Mode Ultrasound Imaging

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Background—Our aim was to compare common carotid mean wall thickness (MWT) measurements by 3.0-T MRI with B-mode ultrasound common carotid intima-media thickness (CCIMT) measurements, a validated surrogate marker for cardiovascular disease.

Methods and Results—B-mode ultrasound and 3.0-T MRI scans of the left and right common carotid arteries were repeated 3 times in 15 healthy younger volunteers (age, 26 ± 2.6 years), 15 healthy older volunteers (age, 57 ± 3.2 years), and 15 subjects with cardiovascular disease and carotid atherosclerosis (age, 63 ± 9.8 years). MWT was 0.711 (SD, 0.229) mm and mean CCIMT was 0.800 (SD, 0.206) mm. MWT and CCIMT were highly correlated ($r = 0.89$, $P < 0.001$). The intraclass correlation coefficients for interscan and interobserver and intraobserver agreements of MRI MWT measurements were larger than 0.95 with small confidence intervals, indicating excellent reproducibility. Power calculations indicate that 89 subjects are required to detect a 4% difference in MRI MWT compared with 469 subjects to detect similar differences with ultrasound IMT in follow-up studies.

Conclusions—The study data for carotid MRI and ultrasound IMT showed strong agreement, indicating that both modalities measure the thickness of the intima and media. The advantage of MRI over ultrasound is that the measurement variability is smaller, enabling smaller sample sizes and potentially shorter study duration in cardiovascular prevention trials. (Circ Cardiovasc Imaging. 2009;2:235-242.)

Key Words: atherosclerosis ■ intima-media thickness ■ carotid artery ■ MRI ■ ultrasound

B-mode ultrasound carotid intima-media thickness (IMT) is a widely used and validated noninvasive imaging technique for the assessment of cardiovascular disease (CVD) risk as well as risk modification. IMT is a strong independent predictor for myocardial infarction and stroke and can provide an impression of cardiovascular drug efficacy, or lack of it.$^{1,2}$

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Despite the scientific foundation of IMT measurements, ultrasound has limitations in the imaging of atherosclerosis, inherent to its physical properties. Ultrasound provides 2D pictures of the vessel wall, whereas atherosclerosis is a 3D, irregular, and eccentric disease. In ultrasound, the measured wall thickness and hence its measurement variability is to a large extent dependent on the ability to reproduce the same angle of insonation and finding the exact same anatomic location when performing the repeat scan. Furthermore, ultrasound is hampered by calcifications, which complicate IMT measurements in subjects with more advanced atherosclerosis.

MRI might overcome these limitations because it is a noninvasive technique that provides cross-sectional images of the carotid artery wall with great anatomic detail. In previous studies, MRI has been shown to reproducibly image carotid plaque volume and composition.$^{3–10}$ MRI has also been shown to be capable of assessing the benefit of lipid-modifying drugs on plaque in relatively small sample sizes.$^{11–21}$ However, MRI has not been able to accurately assess the earlier stages of atherosclerosis. In previous studies a large systemic bias was found between carotid MRI and carotid ultrasound.$^{22,23}$ Carotid wall thickness by MRI was markedly larger than ultrasound IMT. Underhill et al$^{23}$ and Crowe et al$^{22}$ proposed that the difference could be explained by the fact that in addition to intima and media, MRI measurements also comprise the adventitial layer. The relatively low MRI resolution was suggested to be a second important factor in the discrepancy between these 2 modalities.

The aim of the present study was to further improve carotid MRI protocols and determine whether MRI can produce a measurement of the carotid wall thickness equivalent to...
carotid ultrasound. We hypothesized that if we increased MRI resolution, absolute mean wall thickness (MWT) values would be in closer proximity to the IMT values and measurements with both modalities would show high correlation. Moreover, they would describe carotid artery wall thickness progression with age similarly. If so, the benefit of MRI over ultrasound is that cross-sectional imaging (MRI) is better in assessing the 3D development of atherosclerosis than longitudinal imaging (ultrasound). Cross-sectional imaging assesses all sides of the artery wall, whereas longitudinal imaging only evaluates a small part of the artery wall and can miss arterial thickening of other parts of the wall. In addition, carotid MRI could potentially have higher reproducibility than ultrasound.

Methods

Subject Population

We selected 15 younger healthy subjects (age range, 18 to 30 years), 15 older healthy subjects (age range, 50 to 70 years), and 15 subjects with CVD. Subjects with CVD were included if they had 30% to 70% carotid artery stenosis on duplex ultrasound. Healthy subjects did not show any signs and/or symptoms of CVD and were not known to have traditional risk factors for CVD. All subjects underwent bilateral carotid MRI and ultrasound scans. Scans were done at 3 different time points, 1 to 3 weeks apart. The scans were performed between March 2007 and August 2008. MRI and ultrasound scans were analyzed off-line using dedicated software. Before the studies began, approval was obtained from the institutional review board of the Academic Medical Center. All subjects gave written informed consent.

Carotid IMT Measurements

Carotid B-mode ultrasound scans of the left and right common carotid arterial far walls were assessed according to a standardized protocol (Figure 1). The sonographer selected the best diastolic image as a Digital Imaging and Communications in Medicine (DICOM) still capture. Selected images were analyzed qualitatively and quantitatively off-line by a certified image analyzer and validated software (eTrack, Department of Physiology and Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands). One image analyst performed all IMT measurements. Image analysis was done by identifying the lumen-intima and the media-adventitia interfaces (upper and lower red lines). Normalized wall index (NWI) was calculated by dividing mean wall area (MWA), and total wall volume (TWV) were calculated. Normalized wall index (NWI) was calculated by dividing the wall area by the outer wall boundary area. We also calculated the MWT of the far wall segment (MWTfar) to enable a direct comparison of the same arterial segment measured by MRI and ultrasound. We defined the far wall segment on the MRI images between 90° and 135° for the right carotid artery and between 225° and 270° for the left carotid artery, counting clockwise. Signal-to-noise ratios (SNR) were calculated as SNR=S/σ, where S is the true signal intensity corrected for the noise contribution and σ is the true SD of the noise.

3.0-T MRI

MRI scans were obtained on a 3.0-T whole-body scanner (3.0-T Intera, Philips Medical Systems, Best, The Netherlands), using a single-element microcoil (Philips, Hamburg, Germany) with a diameter of 5 cm. Axial T1-weighted turbo spin echo image stacks were acquired at end-diastole using double inversion recovery preparation (Figure 2). Sequence parameters were slice thickness, 3 mm; imaging matrix size, 240; field of view, 60×60 mm; noninterpolated pixel size, 0.25×0.25 mm; echo time, 9 ms; repetition time according to the subjects heart rate, ~900 ms; echo train length, 7; and echo train duration, 63 ms. Active fat suppression (spectral attenuated inversion recovery technique) was applied to improve the definition of the outer wall boundary and avoid chemical shift artifacts. All imaging was performed with cardiac gating.

To localize the left and right common carotid arteries and carotid bifurcation, axial magnetic resonance angiography images were acquired using a time of flight sequence. These images together with projection images were used for positioning the scan planes perpendicular to the vessel at a predefined distance distal to the flow divider.

Eight slices were scanned of the distal 2.4 cm of the left and right common carotid arteries. Each carotid was scanned individually. A total of 16 images were obtained per scan. The slices were located from 15 mm to 39 mm proximal to the carotid flow divider. All images were saved in DICOM format. Standardized equipment and protocols were used for image storage and data management.

To assess the influence of the acquisition matrix and ECG gating on arterial wall measurements, we imaged the carotid artery at different settings in 5 subjects. We varied slice resolution from 0.65 mm to 0.50, 0.25, and 0.20 mm, all with 3-mm slice thickness. At 0.25 mm in-plane resolution, we also imaged with slice thickness of 2 mm. In addition, all imaging was performed with and without cardiac gating at all mentioned in-plane resolutions at a slice thickness of 3 mm for all subjects.

3.0-T MRI Image Analysis

Semiautomated qualitative and quantitative image analyses were performed using semiautomated measurement software (VesselMass, Leiden University Medical Center, Leiden, The Netherlands). Two readers analyzed all images to assess interobserver variability. One reader analyzed all the images twice to assess intraobserver variability. To reduce recall bias, the second reading took place at least 2 months after the first reading. The readers were blinded from previous MRI measurements. Automated tracings of the lumen wall boundaries and the outer wall boundaries (Figure 2) were performed with VesselMass software. If necessary, the automated traced boundaries could be manually corrected. The software algorithm for boundary detection is described elsewhere. MWT, mean wall area (MWA), and total wall volume (TWV) were calculated. Normalized wall index (NWI) was calculated by dividing the wall area by the outer wall boundary area. We also calculated the MWT of the far wall segment (MWTfar) to enable a direct comparison of the same arterial segment measured by MRI and ultrasound. We defined the far wall segment on the MRI images between 90° and 135° for the right carotid artery and between 225° and 270° for the left carotid artery, counting clockwise. Signal-to-noise ratios (SNR) were calculated as SNR=S/σ, where S is the true signal intensity corrected for the noise contribution and σ is the true SD of the noise.
Because the probability density function for the signal magnitude for a single-receiver system follows a Rayleigh distribution, the relation between $\sigma$ and the measured SD of the noise ($SD_n$) is $SD_n = 0.655\sigma$.\textsuperscript{28} Corrected signal intensity $S$ was obtained from the measured magnitude signal ($S_m$) and the measured magnitude of the background noise ($S_n$) and the SD ($SD_n$) of the background noise were measured in a region of interest free of signal and free of artifacts in the corner of the image. Contrast-to-noise ratios (CNR) between wall and lumen were calculated as $\text{CNR} = \frac{\text{SNR}_{\text{wall}}}{\text{SNR}_{\text{lumen}}}$.\textsuperscript{30}

**Statistical Analysis**

Continuous variables are expressed as mean±SD. The SD of the paired differences (SDpd) and the coefficients of variation (COV) were calculated for MWT, MWA, TWV, NWI, and CCIMT. COV was calculated by dividing the SDpd by the mean value of the population for each parameter. Pearson correlation was used to determine the correlation between MWT, MWTfw, and CCIMT. A Bland-Altman plot was used to test for systematic bias between MWTfw and CCIMT. The agreement between successive MRI and ultrasound scans was assessed using intraclass correlation coefficients (ICC) and Bland-Altman plots. The agreement between successive MRI analysis between observers and within one observer was also assessed using ICC(r) and Bland-Altman plots.

The MWA values at different resolutions were compared by analyses of repeated measures using a linear mixed model. MWA values at 0.65 mm resolution were used as the reference. Variation in slice thicknesses and ECG-gated and nongated images were also compared by using a paired 2-tailed Student $t$ test, with $\alpha<0.05$ to represent statistical significance. All statistical analyses were done using SPSS version 16.0 for Windows.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

**Results**

**Patient Characteristics**

Three ultrasound and MRI scans were made of 45 subjects. Fifteen were healthy younger subjects (<30 years), 15 were healthy older subjects (50 to 75 years), and 15 were subjects with CVD and carotid atherosclerosis, defined as 30% to 70% carotid stenosis on ultrasound duplex. The population consisted of 20 women and 25 men, and gender was equally distributed over the 3 groups. The mean The Prospective Cardiovascular Munster Study (PROCAM) risk score for the healthy subjects was 1.9 (SD, 3.4). Patient characteristics are shown in Table 1.

**Imaging Data**

Of all 2160 MR images, 13 (0.6%) were inadequate for image analysis. Mean SNR of the arterial wall was 28.6 (SD, 12.9). Mean CNR between the arterial wall and arterial lumen was 19.0 (SD, 9.3). For SNR and CNR calculations, all 2160 images were evaluated. Mean SNR was higher and mean CNR was equal to previously published values.\textsuperscript{30} Acquisition time was approximately 30 seconds per slice, depending on the heart rate, and total scan time was approximately 45 minutes.

A total of 270 ultrasound images were made, of which all images were adequate for image analysis. The average total ultrasound scan time was approximately 20 minutes.

Mean values (±SD) of MWT, MWTfw, MWA, TWV, NWI, and CCIMT of the initial scan set for the younger subjects, older subjects, and subjects with CVD are shown in Table 1.
The difference in MWT between the younger and older healthy subjects was 0.235 mm (SD, 0.037; \( P/H11001 \)). The difference in MWT between the older subjects with and without CVD was 0.202 mm (SD, 0.130; \( P/H11004 \)).

The SD of the paired differences between the initial and the repeat MRI and ultrasound scans of all 135 scan sets are shown in Table 2. Table 2 also shows the ICCs with 95% confidence intervals for the interscan, interobserver, and intraobserver variability. For the MRI measurements, all ICC values are >0.95, with narrow confidence intervals. The Bland-Altman plots for MWA interscan, interobserver, and intraobserver variability display no fixed or proportional bias (Figure 3).

Correlations between MWT, MWT\(_{fw}\) and CCIMT measurements are shown in Figure 4. MWT and MWT\(_{fw}\) showed high correlation with CCIMT. The Bland-Altman analysis of MWT\(_{fw}\) versus CCIMT is shown in Figure 5. This figure shows a systematic downward bias in the MWT\(_{fw}\) measurement compared with the CCIMT measurements, with a mean difference of \(-0.084\) mm (SD, 0.114 mm, \( P/H11001 \)) in a paired \( t \) test.

Influence of Sequence Parameters on Arterial Wall Dimensions

We imaged the carotid arteries of 5 subjects with and without ECG gating and at various resolutions and slice thicknesses. MWA decreased \(1.8\) mm\(^2\) (SD, \(2.1\) mm\(^2\); \( P/H11001 \)) when ECG gating was used. This decrease was present at all resolutions.

MWA increased with decreasing resolution; MWA was \(19.0\) mm\(^2\) (SD, \(1.5\) mm\(^2\)) at in-plane resolution of \(0.65\) mm and served as the reference. MWA decreased \(4.4\) mm\(^2\) (SD, \(1.3\) mm\(^2\); \( P/H11002 \)) at in-plane resolution of \(0.50\) mm, \(8.3\) mm\(^2\) (SD, \(1.9\) mm\(^2\); \( P/H11001 \)) at in-plane resolution of \(0.25\) mm, and \(7.5\) mm\(^2\) (SD, \(2.9\) mm\(^2\); \( P/H11001 \)) at in-plane resolution of \(0.20\) mm. MWA did not change when we varied slice thickness from 3 mm to 2 mm; the difference was \(0.2\) mm\(^2\) (SD, \(0.4\) mm\(^2\), \( P/H11002 \)).

Discussion

In the present study we showed that data of carotid MRI and ultrasound IMT showed strong agreement, indicating that both modalities measure the thickness of the intima and media. However, the measurement variability of the MRI was lower compared with the ultrasound technique. The high degree of correlation of MRI MWT to ultrasound IMT, an accepted surrogate marker for CVD, combined with a lower

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<th>Table 2. Measurement Variability of the Different MRI Measurements</th>
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<td><strong>Interscan variability</strong></td>
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| **Interobserver variability**                                |
| All subjects                                                 |
| TWV, mm\(^2\)                                                | 0.99 (0.98–0.99) |
| MWA, mm\(^2\)                                                | 0.99 (0.98–0.99) |
| NWI, mm                                                      | 0.97 (0.97–0.99) |
| MWT, mm                                                     | 0.94 (0.92–0.96) |
| SDpd                                                         |
| Younger subjects                                             | 23.9 mm\(^3\) |
| Middle-aged subjects                                         | 24.9 mm\(^3\) |

| **Intraobserver variability**                                |
| All subjects                                                 |
| TWV, mm\(^2\)                                                | 0.97 (0.95–0.98) |
| MWA, mm\(^2\)                                                | 0.97 (0.95–0.98) |
| NWI, mm                                                      | 0.96 (0.94–0.97) |
| MWT, mm                                                     | 0.94 (0.92–0.96) |
| SDpd                                                         |
| Younger subjects                                             | 23.9 mm\(^3\) |
| Middle-aged subjects                                         | 24.9 mm\(^3\) |

| **COV**                                                      |
| All subjects                                                 |
| TWV, mm\(^2\)                                                | 6.5% |
| MWA, mm\(^2\)                                                | 6.5% |
| NWI, mm                                                      | 6.1% |
| MWT, mm                                                     | 6.9% |
| CCIMT                                                        | 12.8% |

**TChol** indicates total cholesterol; **LDL-c**, low-density lipoprotein cholesterol; **HDL-c**, high-density lipoprotein cholesterol; **TG**, triglycerides; **hsCRP**, high-sensitivity C-reactive protein; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **BMI**, body mass index.
variability for MRI, shows that carotid MRI holds potential as a surrogate marker for CVD and may allow smaller sample sizes and shorter study duration in future cardiovascular prevention trials.

The fact that the absolute values of MRI measurements were very similar to the ultrasound results, we found MWT to be on average 0.084 mm smaller than IMT measurements. The exact reason for these lower values by MRI remains unclear. Most likely, the latter pertains to a difference between the MRI and ultrasound image analysis algorithms, resulting in a consistent, minor difference. Since the discrepancy between modalities is small and independent of the wall thickness, it bears little relevance for the assessment of cardiovascular risk and risk modification, in our opinion.

The reproducibility of IMT measurements has enabled IMT to be used as a surrogate marker for cardiovascular disease in epidemiological and intervention trials. However, reproducibility of IMT is insufficient for individual risk assessment, and the number of subjects needed to assess cardiovascular drug efficacy is relatively large. Moreover, high reproducibility of measurement tools is always in demand because it contributes to higher precision and reproducibility of clinical trials. The results of this study demonstrate that measurement of carotid artery wall dimensions by MRI has high interscan reproducibility, exceeding that of IMT measurements in this study and that of recently published IMT studies. The interscan COV for MRI is about half of the interscan COV for ultrasound in the current study (6.5% versus 12.8%). Furthermore, MRI interscan reproducibility was equivalent in all 3 populations that were scanned and was not affected by age or the severity of atherosclerosis.

The interscan reproducibility of our data also exceeds that of the previously published carotid MRI data by Varghese et al and Alizadeh et al. Varghese et al assessed the interstudy reproducibility in 10 subjects with evidence of carotid artery atherosclerosis and 16 older healthy volunteers and found the mean SD of the paired difference of MWA between scans to range from 33 mm$^2$ to 38 mm$^2$, whereas in our data it was 22.9 mm$^2$. Alizadeh et al studied 10 healthy subjects in the age range of 25 to 79 years (mean age, 57 years) and reported mean SDs of the paired difference between scans of MWA to range from 5.9 mm$^2$ to 9.8 mm$^2$, whereas in our data it was 1.0 mm$^2$.

Last, the interobserver and intraobserver reproducibility of our data were high, due to the use of semiautomated software analysis. These findings are consistent with previously published data. Power calculations indicate that a sample size of 89 subjects would be needed to detect a 4% (0.03 mm) difference in MWT by carotid MRI compared with a sample size of 469 subjects to detect a similar difference with ultrasound.

This issue, we assessed the influence of resolution and ECG gating on arterial wall dimensions. We found MWA to decrease with increasing resolutions and with ECG gating. This confirms that the findings of Underhill et al and Crowe et al were indeed due to an overestimation of MRI-measured IMT, probably due to a lower spatial resolution and non–ECG-gated imaging. To completely resolve this issue, additional studies are needed comparing MRI and ultrasound measurements with the histology of specimens of carotid arteries.

Figure 3. Bland-Altman plots of interscan (A), interobserver (B), and intraobserver (C) variability of mean wall area measurements of all 3 scans. The solid line is the mean of the differences between the 3 scans; the 95% prediction intervals are drawn as dashed lines. Paired t tests to assess systemic bias were not significant.
Study Limitations

A potential limitation of this study is that we defined the far wall segment on the MRI images between 225° and 270° for the left carotid artery and between 90° and 135° for the right carotid artery, counting clockwise from the top. In our opinion, these were the segments that best resemble the far wall segment as measured by ultrasound. In ultrasound imaging, the distal 1 cm of the common carotid artery just proximal to the carotid dilation was imaged. We aimed to image the similar section of the carotid by MRI. To be as close as possible to the segment imaged by ultrasound, we chose to image 15 to 39 mm proximal to the carotid bifurcation. It is, however, impossible to pinpoint the exact location of the ultrasound measurement.

Another potential limitation of this study is that we only assessed the common carotid artery with MRI and not the carotid bulb and internal carotid artery. However, common carotid artery IMT is a valid surrogate end point for cardiovascular disease, as epidemiological data indicate that the common carotid IMT is a good predictor for coronary heart disease and stroke. Moreover, IMT of the common carotid artery segment has proved a robust measurement for detecting drug efficacy in many intervention trials.

Conclusion

Absolute values for carotid MRI and ultrasound measurements were similar and highly correlated, whereas the variability of the MRI measurement was smaller than for ultrasound. The high correlation of MRI with ultrasound implies that carotid MRI can expand on the extensive experience of prospective ultrasound IMT studies and intervention trials, which have resulted in acceptance of IMT as a surrogate marker for CVD risk. In addition, due to its improved variability, MRI will enable smaller sample sizes in cardiovascular prevention studies. The combination of lower variability and a decreased number of subjects included will also allow for a reduction in overall trial duration if MRI is used.

These data challenge us to further develop carotid MRI in standardized protocols to become a surrogate marker for cardiovascular events, with the potential to substitute larger IMT studies with smaller and less time-consuming carotid MRI studies.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Atherosclerosis imaging of the carotid arteries can be used to assess both cardiovascular disease risk as well as the efficacy of novel cardiovascular drugs. Presently, the B-mode ultrasound measurement of carotid intima-media thickness is the most widely available and best validated atherosclerosis imaging technique. Nonetheless, as atherosclerosis is a 3D, irregular, and eccentric disease process, longitudinal 2D ultrasound carotid intima-media thickness measurements of the arterial wall have their inherent limitations. We set out to compare high-resolution B-mode ultrasound carotid intima-media thickness with carotid 3.0-T MRI measurements in humans. We observed that both MRI and ultrasound measurements provide similar results in terms of carotid arterial wall thickness. MRI, however, showed a much better reproducibility than ultrasound. The 3D, highly reproducible MRI may provide a better surrogate for the evaluation of the efficacy of antiatherosclerotic drugs.
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