In vivo quantification of carotid artery wall dimensions: 3.0 Tesla MRI versus B-mode ultrasound imaging.

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Subject Codes:
[150] Imaging
[30] MRI
[33] Other diagnostic testing (ultrasound)
ABSTRACT

Background  Our aim was to compare common carotid Mean Wall Thickness (MWT) measurements by 3.0 Tesla MRI to B-mode ultrasound (US) common carotid intima-media thickness (CCIMT) measurements, a validated surrogate marker for cardiovascular disease (CVD).

Methods and results  3.0 Tesla MRI and B-mode ultrasound scans of the left and right common carotid arteries were repeated three times in 15 healthy younger volunteers (aged 26 ± 2.6 years), 15 healthy older volunteers (aged 57 ± 3.2 years) and 15 subjects with CVD and carotid atherosclerosis (aged 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 inter- 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 to 409 subjects to detect similar differences with US IMT in follow-up studies.

Conclusion  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 US is that the measurement variability is smaller, enabling smaller sample sizes and potentially shorter study duration in cardiovascular prevention trials.

Keywords (5)  Atherosclerosis, intima-media thickness, carotid artery, magnetic resonance imaging, ultrasound.
INTRODUCTION

B-mode ultrasound (US) carotid intima-media thickness (IMT) is a widely used and validated non-invasive 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.\textsuperscript{1,2}

Despite the scientific foundation of IMT measurements, ultrasound has limitations in the imaging of atherosclerosis, inherent to its physical properties. US provides two-dimensional pictures of the vessel wall, while atherosclerosis is a three-dimensional, 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, US is hampered by calcifications which complicates IMT measurements in subjects with more advanced atherosclerosis.

Magnetic resonance imaging (MRI) might overcome these limitations as it is a non-invasive technique that provides cross-sectional images of the carotid artery wall with great anatomical detail. In previous studies, MRI has been shown to reproducibly image carotid plaque volume and composition.\textsuperscript{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.\textsuperscript{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 US.\textsuperscript{22,23} Carotid wall thickness by MRI was markedly larger than US IMT. Underhill \textit{et al.} and Crowe \textit{et al.} 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 two 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 US. 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 US is that cross-sectional imaging (MRI) is better in assessing the three-dimensional development of atherosclerosis than longitudinal imaging (US). Cross-sectional imaging assesses all sides of the artery wall, while 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 US.

METHODS

Subject population

We selected fifteen younger healthy subjects (range 18 to 30 years), fifteen older healthy subjects (range 50 to 70 years) and 15 subjects with cardiovascular disease (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 with traditional risk factors for CVD. All subjects underwent bilateral carotid MRI and US scans. Scans were done at three different time points, one to three weeks apart. The scans were performed between March 2007 and August 2008. MRI and US scans were analyzed off-line
using dedicated software. Prior to the studies, approval was obtained of the Institutional Review Board of the AMC. All subjects gave written informed consent.

**Carotid intima-media thickness measurements**

Carotid B-mode ultrasound scans of the left and right common carotid artery far wall were assessed according to a standardized protocol (Figure 1). The sonographer selected the best diastolic image as a 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 did all IMT measurements. Image analysis was done by identifying the lumen-intima and the media-adventitia boundaries of the carotid arterial far walls. The method has been described elsewhere. Common Carotid Intima-Media Thickness (CCIMT) was calculated as the average of the mean IMT of the far wall of the distal 1 cm of the left and right common carotid artery.

**3.0 Tesla magnetic resonance imaging**

Magnetic resonance imaging scans were obtained on a 3.0 Tesla whole-body scanner (3.0 Tesla Intera, Philips Medical Systems, Best, The Netherlands), using a single-element microcoil (Philips, Hamburg, Germany) with a diameter of five centimeters. Axial T1-weighted Turbo Spin Echo (TSE) image stacks were acquired at end-diastole using double inversion recovery (DIR) preparation (Figure 2). Sequence parameters were: slice thickness 3 mm, imaging matrix size 240, FOV of 60 x 60 mm, non-interpolated pixel size 0.25 x 0.25 mm, TE 9 ms, TR according to the subjects’ heart rate (approximately 900 ms), echo train length 7, echo train duration 63 ms. Active fat suppression (spectral attenuated inversion
recovery (SPAIR) 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 artery and carotid bifurcation, axial Magnetic Resonance Angiography (MRA) images were acquired using a Time of Flight (TOF) 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 artery. 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 in plane resolution from 0.65 mm to 0.50 mm, 0.25 mm and 0.20 mm, all with 3 mm slice thickness. At 0.25 mm in plane resolution we also imaged with slice thickness 2 mm. In addition, all imaging was performed with and without cardiac gating at all mentioned in plane resolutions at slice thickness 3 mm for all subjects.

3.0 Tesla MRI image analysis

Semi-automated qualitative and quantitative image analysis were performed using semi-automated measurement software (VesselMass, Leiden University Medical Center, Leiden, The Netherlands). Two readers analyzed all images to assess inter-observer variability. One reader analyzed all the images twice to assess intra-observer variance. 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. The VesselMass software performed automated
tracing of the lumen-wall boundaries and the outer wall boundaries (Figure 2). If necessary, the automated traced boundaries could be manually corrected. The software algorithm for boundary detection is described elsewhere. Mean Wall Thickness (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 Mean Wall Thickness of the “far wall segment” (MWT_{fw}) to enable a direct comparison of the same arterial segment measured by MRI and US. 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 = \( \frac{S}{\sigma} \), where \( S \) is the true signal intensity corrected for the noise contribution, and \( \sigma \) is the true standard deviation (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 (\( \sigma_n \)) is \( \sigma_n = 0.655 \sigma \).\(^{28}\) Corrected signal intensity \( S \) was obtained from the measured magnitude signal (\( S_m \)) and the measured magnitude of the background noise (\( S_n \)): \( S = (S_m^2 - S_n^2)^{1/2} \).\(^{29}\) The magnitude (\( S_n \)) and the SD (\( \sigma_n \)) 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 CNR = SNR_{wall} – SNR_{lumen}.

**Statistical analysis**

Continuous variables are expressed as mean ± SD. The SD of the paired differences (SDpd) and the coefficients of variation (COV) between the initial and the repeat scans 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’s correlation was used to determine the correlation between MWT, MWT_{fw} and CCIMT. A Bland-Altman plot was...
used to test for systematic bias between MWT$_{fw}$ and CCIMT. The agreement between successive MRI and US scans was assessed using intraclass correlation coefficients (ICC (r)) and Bland-Altman plots. The agreement between successive MRI analysis between observers and within one observer were also assessed using ICC (r) and Bland-Altman plots.

The MWA values at different resolutions were compared by analyses of repeat 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 non-gated images were also compared by using a paired two-tailed Student’s t-test, with $\alpha < 0.05$ to represent statistical significance.

All statistical analyses were done using SPSS (Statistical Package for the Social Sciences) 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 US and MRI scans were made of forty-five subjects. Fifteen were healthy younger subjects (<30 years), fifteen were healthy older subjects (50 to 75 years) and fifteen were subjects with CVD and carotid atherosclerosis, defined as 30 to 70% carotid stenosis on US duplex. The population consisted of 20 females and 25 males and gender was equally distributed over the three groups. The mean 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 images (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. Acquisition time was around 30 seconds per slice depending on the heart rate and total scan time was approximately 45 minutes.

A total of 270 US images were made, of which all images were adequate for image analysis. Average total US scan time was around 20 minutes.

Mean values (±SD) of MWT, MWT<sub>fw</sub>, 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<0.001). The difference in MWT between the older subjects with and without CVD was 0.202 mm (SD 0.130, p=0.004).

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

Correlations between MWT, MWT<sub>fw</sub> and CCIMT measurements are shown in Figure 4. MWT and MWT<sub>fw</sub> showed high correlation with CCIMT. The Bland-Altman analysis of MWT<sub>fw</sub> versus CCIMT is shown in Figure 5. This figure shows a systematic downward bias in the MWT<sub>fw</sub> measurement compared to the CCIMT measurements, with a mean difference of -0.084 mm (SD 0.114 mm, p<0.001 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 mm² (SD 2.1 mm², p=0.001) when ECG gating was used. This decrease was present at all resolutions.

MWA increased with decreasing resolution; MWA was 19.0 mm² (SD 1.5 mm²) at in plane resolution 0.65 mm and serves as the reference. MWA decreased 4.4 mm² (SD 1.3 mm², p=0.002) at in plane resolution 0.50 mm, 8.3 mm² (SD 1.9 mm², p=0.001) at in plane resolution 0.25 mm, and 7.5 mm² (SD 2.9 mm², p=0.004) at in plane resolution 0.20 mm. MWA did not change when we varied slice thickness from 3 mm to 2 mm; difference 0.2 mm² (SD 0.4 mm², p=0.24).

DISCUSSION

In the present study we show 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 to the US technique.

The high degree of correlation of MRI MWT to US IMT, an accepted surrogate marker for CVD, combined with a lower 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 US results is in contradiction to previously published data by Underhill et al. and Crowe et al. Both authors found MRI measurements to be markedly larger than IMT by US and proposed that in addition to intima and media, MRI measurements also incorporated the adventitial layer.22,23
MRI resolution was suggested to be a second confounding factor in the discrepancy between the two modalities. To further clarify 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 intima-media thickness probably due to a lower spatial resolution and non-ECG gated imaging. To completely resolve this issue, additional studies are needed comparing MRI and US measurements to histology of specimens of carotid arteries.

Although the absolute values of MRI measurements were very similar to the US 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 US 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 as 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 three 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.\textsuperscript{39,40} and Alizadeh et al.\textsuperscript{41} 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 standard deviation of the paired difference of MWV between scans to range from 33 mm\textsuperscript{3} to 38 mm\textsuperscript{3}, while in our data it was 22.9 mm\textsuperscript{3}. Alizadeh et al. studied 10 healthy subjects in the age range of 25 to 79 years (mean age 57 years) and reported mean standard deviations of the paired difference between scans of MWA to range from 5.9 mm\textsuperscript{2} to 9.8 mm\textsuperscript{2}, while in our data it was 1.0 mm\textsuperscript{2}.

Last, the inter-observer and intra-observer reproducibility of our data were high, due to the use of semi-automated software analysis. These findings are consistent with previously published data.\textsuperscript{25,27}

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 to a sample size of 469 subjects to detect a similar difference with US.

**Study limitations**

A potential limitation of this study is that we defined the far wall segment on the MRI images between 225\degree and 270\degree for the left carotid artery and between 90\degree and 135\degree 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 US. 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. In order 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 US 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 endpoint for cardiovascular disease, as epidemiological data indicate that common carotid IMT is a good predictor for coronary heart disease and stroke\(^2\). Moreover, IMT of the common carotid artery segment has proved a robust measurement for detecting drug efficacy in many intervention trials\(^1\).

**Conclusion**

Absolute values for carotid MRI and US measurements were similar and highly correlated, whereas the variability of the MRI measurement was smaller than for US. The high correlation of MRI with US implies that carotid MRI can expand on the extensive experience of prospective US IMT studies and intervention trials, which have resulted in acceptance of IMT as surrogate marker for CV-risk. In addition, due to its improved variability, MRI will enable smaller sample sizes in cardiovascular prevention studies. The combination of lower variability and 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 CV events with the potential to substitute larger IMT studies with smaller and less time-consuming carotid MRI studies.

**Acknowledgements**
R. Duivenvoorden, MD, E. de Groot, MD PhD, and A.J. Nederveen, PhD, wrote the manuscript and were involved in data analysis and data acquisition. B.M. Elsen, MD, was involved in data analysis, R.J. van der Geest, Msc, J.S. Laméris, MD PhD, E.S.G. Stroes, MD PhD and J.J.P. Kastelein, MD PhD, critically reviewed the manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Disclosures**

None.

**Reference List**


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# Tables

## Demographics

<table>
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<tr>
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<th>Healthy younger subjects</th>
<th>Healthy older subjects</th>
<th>Subjects with CVD</th>
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<tr>
<td>Age (years)</td>
<td>25.9 (2.6)</td>
<td>57.4 (3.2)</td>
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<td>TChol (mmol/l)</td>
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## MRI measurements

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<tr>
<td>TWV (mm$^3$)</td>
<td>243.0 (36.5)</td>
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<td>MWA (mm$^2$)</td>
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<td>NWI</td>
<td>0.256 (0.024)</td>
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<td>MWT (mm)</td>
<td>0.487 (0.047)</td>
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<td>MWTfw (mm)</td>
<td>0.497 (0.050)</td>
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## Ultrasound measurements

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<td>CCIMT (mm)</td>
<td>0.605 (0.086)</td>
<td>0.858 (0.217)</td>
<td>0.936 (0.119)</td>
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Table 1. Demographics and mean (± SD) values of common carotid artery wall dimensions measured by 3.0 Tesla MRI and US tabulated for the initial session. TWV is Total Wall Volume (mm$^3$), MWA is Mean Wall Area (mm$^2$), NWI is Normalized Wall Index, MWT is Mean Wall Thickness (mm), MWTfw is Mean Wall Thickness of the far-wall segment (mm), CCIMT is Common Carotid Intima-Media Thickness (mm), CVD is cardiovascular disease.
Table 2. Measurement variability of the different MRI measurements. Intra-class correlation coefficient values (95% Confidence intervals in parentheses), coefficient of variation (COV) values and SD’s of the paired differences between scans (SDpd) for all subjects are shown. The SDpd’s are also shown per group. MWT is Mean Wall Thickness, MWA is Mean Wall Area, TWV is Total Wall Volume, NWI is Normalized Wall Index, CCIMT is Common Carotid Intima-Media Thickness.

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<th>MWA (mm²)</th>
<th>NWI (%)</th>
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Figure Legends

**Figure 1.** B-Mode ultrasound image and image analysis of the common carotid artery.

High resolution 15MHz B-mode ultrasound image of the distal common carotid artery far-wall in a healthy 27 year old volunteer. The vertical arrow indicates the carotid dilatation, just proximal of the carotid bulb. The right picture shows the Intima-Media Thickness (IMT) image analysis. IMT is defined as the distance between the lumen-intima and the media-adventitia interfaces (upper and lower red lines).

**Figure 2.** 3.0 Tesla MRI image and image analysis of the common carotid artery.

Cross-sectional images of the left common carotid artery wall of a young subject (A) and an older subject (B). The left and right lowest pictures show the image analysis. The inner and outer borders of the carotid artery are semi-automatically detected with dedicated software (VesselMass, Leiden University Medical Center, Leiden, The Netherlands). The Mean Wall Area (MWA) and Total Wall Volume (TWV) have been calculated from the difference between the inner and outer borders. The Mean Wall Thickness (MWT) is defined as the distance between the inner and outer border (indicated by the yellow lines). The artery wall is divided into 8 segments, which can be analyzed separately. The segment indicated by the arrow was considered the far wall segment of the left artery.

**Figure 3.** Bland-Altman plots of (A) Interscan, (B) Inter-Observer and (C) Intra-Observer Variability of MWA measurements of all three 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.
Figure 4. Comparison of CCIMT with MWT (left) and MWTfw (right) of the initial scan.

The US data have a very high correlation with the MRI measurements of the mean wall thickness and the far wall thickness.

Figure 5. Bland–Altman analysis of MWTfw versus CCIMT of all three scans. A systematic downward bias of MWTfw compared to IMT can be observed of -0.084 mm (SD 0.114 mm). The solid line is the mean of the differences between MWTfw and CCIMT; the 95% prediction intervals are drawn as dashed lines.
In vivo quantification of carotid artery wall dimensions: 3.0 Tesla MRI versus B-mode ultrasound imaging.

Raphael Duivenvoorden, Eric de Groot, Bart M. Elsen, Johan S. Laméris, Rob J. van der Geest, Erik S. Stroes, John J.P. Kastelein and Aart J. Nederveen

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