Carotid imaging in cardiovascular risk assessment

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CHAPTER 4

Carotid Artery Diameter, Wall Thickness and Wall Area by MRI at 3-Tesla: Comparison with Ultrasound

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ABSTRACT

Purpose

To compare MRI based measurements of the lumen diameter, vessel wall thickness and wall area of the carotid artery to ultrasound based measurements of the lumen diameter and intima-media thickness (IMT) in asymptomatic young adult and middle aged subjects.

Subjects and Methods

Ultrasound and MRI at 3-Tesla of the left common carotid artery were performed in 39 healthy subjects. The mean age in group 1 (n=28) was 51 years and 25 years in group 2 (n=11). The lumen diameter, mean wall thickness and wall area were measured in a predefined segment of the carotid artery using a black blood fast gradient MRI sequence. The lumen diameter and IMT were measured by ultrasound in the same vessel segment. Correlation analysis and Bland & Altman plots were used to compare MRI and ultrasound measurements.

Results

Measurements of the carotid lumen diameter by ultrasound and MRI showed high agreement (intraclass correlation coefficient 0.882). Highly significant correlations were found between IMT and MRI measurements of mean wall thickness and wall area ($r=0.84$, $p<0.001$ and 0.74, $p<0.001$, respectively). Middle aged asymptomatic subjects had significant higher IMT, wall thickness and wall area values as compared to healthy young adults ($p<0.001$).

Conclusion

MRI and ultrasound show excellent agreement for measuring the carotid lumen diameter. MRI measurements of wall thickness and wall area correlate well with IMT. Asymptomatic subjects reveal an age-dependent increase in IMT, wall thickness and wall area.

INTRODUCTION

Carotid intima-media thickness (IMT) by ultrasound is a widely accepted surrogate marker for cardiovascular disease. It has been extensively documented that carotid atherosclerosis is related to cardiovascular risk, coronary and cerebrovascular atherosclerosis (89) (90) (91) (92). Large epidemiological studies have shown that the presence of carotid atherosclerosis as measured by high resolution ultrasound is related to the occurrence of future cardiovascular events (5) (6) (7) (8)((9). These data have prompted the American Heart Association (93), The European Society of Hypertension (94) and the European Society of Cardiology (9) to advocate the use of carotid imaging in cardiovascular risk assessment and as an intermediate endpoint in clinical trials. Both applications of carotid ultrasound have limitations. Additional predictive value of IMT measurement above risk assessment algorithms based on traditional risk factors seems to be a consistent finding, however the magnitude of the improvement may be marginal. (95) (96) (97) (98). These data make its clinical relevance for risk restratification in individual patients questionable. Studies using carotid ultrasound as an endpoint require relatively large sample sizes partly due slow progression rates of IMT and the cross-sectional images ultrasound provides limiting full quantification of the vessel wall geometry. Moreover many ultrasound protocols do not take carotid plaques into account.

Magnetic resonance imaging (MRI) has recently emerged as a reproducible and reliable imaging modality for the assessment of atherosclerosis (17) (100) (101). Serial MRI of the vessel wall allows for monitoring of carotid atherosclerosis in relatively small samples of the population owing to the lower interscan variability of the MRI measurements as compared to those by ultrasound. (40) (41) Furthermore, MRI provides a circumferential image of the vessel, which may potentially better represent wall pathology such as eccentric arterial remodelling as compared to luminography and ultrasound.

The role of 3T carotid MRI as a predictor of future vascular events is still unknown due to a lack of clinical outcome studies. There are studies associating MRI-based carotid plaque presence and characteristics to stroke risk (101) but these findings are all in high-risk patients where carotid plaques are already present. Data on vessel wall geometry parameters in early atherosclerosis (i.e. no plaque presence) and future cardiovascular events are lacking. Regarding ultrasound-based IMT measurements there is a broad consensus on threshold values for higher cardiovascular risk (usually >0.9mm at the level of the common carotid artery). Its equivalent for MRI based measurements is yet not defined

The purpose of the current study is to evaluate the potential of 3T carotid MRI as a biomarker for early atherosclerosis in absence of carotid plaque. To this end, a head-to-head comparison was performed of measurements of the carotid lumen diameter and IMT by ultrasound and the lumen diameter, wall area and wall thickness by black blood fast gradient MRI at 3-Tesla in an population with no evidence of carotid plaque.

Furthermore, direct comparison of the two imaging modalities could offer insight on cut-off values for higher cardiovascular risk.

METHODS

Study Design & Subjects

A series of 41 subjects were prospectively included in the study over a 1 year period. The time between ultrasound (US) and MRI examination was never more than 2 months. In 2 cases the MRI was not interpretable due to insufficient quality leaving 39 subjects for analysis. Informed consent was obtained and the study protocol was approved by the hospital ethics committee. The sample was comprised of 28 older male subjects with a broad range in cardiovascular risk (group 1), recruited from a separate ongoing randomised clinical trial. The inclusion criterion was the presence of visceral obesity (>94 cm waist circumference). The use of statins or non-steroidal anti-inflammatory drugs, as well as the presence of diabetes mellitus was considered exclusion criteria. In addition, we recruited 11 young healthy subjects (group 2). All subjects were free of clinically manifest cardiovascular disease and the 10-year risk of a coronary event was calculated for group 1 using the Framingham risk score, described in detail elsewhere. (102) Based on age, medical and family history it is assumed all subjects in group 2 are at low cardiovascular risk. The US and MRI scans were performed by fully trained single observers. Both observers were blinded for the results of the scan with the other imaging modality.

Magnetic Resonance Imaging Protocol

Magnetic resonance imaging was performed on a 3-Tesla scanner (Philips, Achieva, Best, The Netherlands). The reproducibility of the technique has been previously reported. (100) In brief, a standard Philips SENSE-flex-M surface coil was used for imaging. The left carotid artery was examined in all subjects. Three fast gradient echo sequence surveys were performed to localize the course of the common carotid artery. Subsequently, five contiguous transverse slices with 2mm slice thickness were acquired, starting from 1cm proximal to the flow divider, thereby covering 1 cm of the common carotid artery. A dual inversion recovery (black-blood), spoiled segmented k-space fast gradient echo sequence with spectral selective fat suppression was used for the acquisition of transverse slices. Images were acquired in cardiac end-diastole at each RR interval using ECG triggering. The following imaging parameters were used: echo time 3.6ms, repetition time (TR) 12ms, flip angle 45 degrees, and 2 signal averages were performed. A re-inversion slice thickness of 3mm was used. The field of view was 140mm. When using a matrix size of 306 the resulting voxel size was 0.46mm x 0.46mm x 2mm. Each MRI study took approximately 30 minutes depending on the cardiac frequency. All images were analyzed by a single observer with 4 years' experience, using the VesselMASS software package, allowing manual tracing of vessel boundaries and automated quantification of lumen diameter, wall area and mean wall thickness. Mean wall thickness (MWT) was calculated by averaging the mean thickness at all 5 slices of the common carotid artery. Vessel wall area (VWA) was quantified by extracting the luminal area from the detected outer vascular boundary at each slice. The sum of these 5 area values was used the outcome parameter VWA. Figure 1 shows a representative example of an MRI scan of the carotid artery.

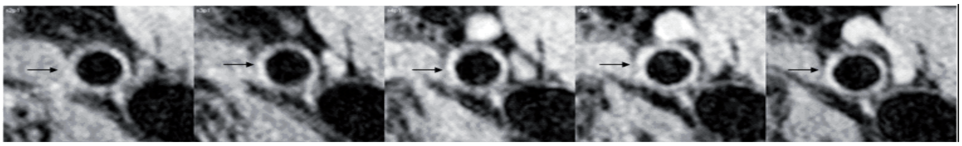

Figure 1 | Representative example of 3-Tesla MRI image of the carotid artery of a 62-year old male subject. Black arrows indicate the carotid artery. Five contiguous transverse slices of 2mm, covering the most distal 1cm of the common carotid artery.

Ultrasound protocol

IMT measurement was performed using an Acuson Sequoia 512 (Siemens Medical Solutions, CA, USA) high-resolution ultrasound machine with an 8MHz linear transducer. One IMT-certified sonographer (4 years of experience) performed all the ultrasounds. First, a transverse scan was performed for orientation, starting at the clavicle and moving cranially up to the mandible, hereby locating the height of the carotid bifurcation. Subsequently, longitudinal images were obtained. This technique allows visualization of two echogenic lines, separated by an anechoic space. It has previously been established that these lines indicate the blood-intima and the media-adventitia interfaces, and that the distance between the lines represents a reliable measure for IMT. (23) The scan included visualization of the near and far walls of the left common carotid artery, at four angles of insonation (anterior, two antero-lateral projections and lateral). The caudal tip of the flow divider was used as the anatomical landmark to localize the most distal 1cm of the common carotid artery. Overall gain settings were kept at 0dB when possible. The sonographer was free to adjust the gain levels if necessary, within the limits of -7dB to 7 dB. The scan was recorded on sVHS video cassettes and digitalized for off-line analysis. IMT values were quantified using computer aided automatic boundary detection where possible and manual adjustment where necessary. Analyses were done by a trained analyst, using the ASM II software package version 1.1364. IMT was defined as the average of the mean values of the common carotid artery, at all four angles. Lumen diameter was also determined at four angles and defined as the distance between the intima-lumen interface of the near wall and the lumen-intima interface of the far wall. Quantification of all parameters was timed to coincide with cardiac end-diastole using an on-screen 3-lead ECG.

Statistical analysis

All data followed normal distribution. The primary analysis was aimed at a comparison of lumen diameter and wall thickness by US and MRI, in which the same geometric parameters (mm) could be compared. The comparison between US and MRI-based quantification of lumen diameter was included to provide data on the technical agreement between the two imaging modalities. A secondary analysis compared US-based thickness (mm) to MRI-based area (mm^2) measurement. Vessel wall area is an important outcome parameter in 3T carotid MRI and its relation to US-based IMT values was deemed to be relevant for interpretation of future studies using 3T carotid MRI. Within-subject differences between US and MRI were evaluated with a T-test. Correlations between US and MRI were calculated using Pearson's correlation coefficients. Extrapolation of normal and high-risk values for MRI parameters was based on linear estimation functions from the US- IMT regression lines. Bland-Altman analyses (24) and intraclass correlations coefficients (ICC) were used to assess agreement of the two imaging modalities, regarding measurement of thickness and lumen diameter within subjects. Two-sided p-values of <0.05 were considered statistically significant. All data are expressed as means and 95% confidence intervals, except in table 1 in which the range is given in parentheses to illustrate the diversity of vascular parameters in the study population.

RESULTS

The technical success rate for completing the MRI examinations was high (39/41 subjects; 95%). Subject characteristics and results are summarized in table 1. The mean lumen diameter measured by US and MRI showed very high agreement,

Table 1 | Values are expressed in means [range].

Variable	Total sample	Group 1	Group 2
N	39	28	11
age (yrs)	51.3 [20-73]	61.8 [54-73]	24.7 [20-39]*
Framingham CHD risk score (%/10yrs)	-	15.8 [6-29]	-
mean IMT; US (mm)	0.76 [0.45-1.36]	0.86 [0.65-1.36]	0.50 [0.45-0.70]*
MWT; MRI (mm)	1.25 [0.72-2.29]	1.40 [0.98-2.29]	0.87 [0.72-1.27]*
VWA; MRI (cm^2)	1.64 [0.67-3.77]	1.90 [1.11-3.77]	0.96 [0.67-1.45]*
lumen diameter; MRI (mm)	6.71 [5.08-8.99]	7.00 [6.68-7.30]	6.00 [5.73-6.28]
lumen diameter; US (mm)	6.71 [5.28-9.00]	7.00 [5.53-9.10]	5.96 [5.28-6.37]

Group1=older subset; group 2=young healthy volunteers. Data show the expected differences between the younger and the older group in vessel wall parameters. No difference was observed between MRI and US in measurement of lumen diameter, confirming dimensional compatibility between the techniques. Asterisk (*) indicates statistically significant difference between group 1 and 2 (p<0.001). CHD=coronary heart disease; IMT=intima-media thickness; MWT=mean wall thickness; VWA=common carotid vessel wall area.

with a mean difference of 0.03mm [-0.16 to 0.11]; p=0.669 and a high intraclass correlation for absolute agreement of 0.882 (p<0.001). The Bland-Altman plot (figure 2) showed no bias, with the mean line corresponding exactly with 0.00 with an acceptable spread around the mean (within 1.96 standard deviations).

IMT values in the total sample ranged from 0.45mm to 1.36mm encompassing subjects with a broad range of the Framingham risk score. The younger subjects (group 2) had a mean IMT of 0.50mm [range: 0.46 to 0.55]. The corresponding mean values for MWT and VWA were 0.87mm [range: 0.72 to 1.27] and 0.96cm^2 [range: 0.67 to 1.45], respectively. Mean IMT, MWT and VWA in group 1 subjects were significantly higher than in group 2 subjects (table 1).

The bivariate correlations between the US and MRI parameters are shown in Table 2 and illustrated in figures 4 & 5. Highly significant correlations were observed for all measures. The statistically significant regression lines between IMT and MRI parameters suggest that the clinical cut-off for IMT of 0.9mm corresponds approximately with a MWT value of 1.45mm (figure 4) and VWA of 2.00cm^2 (figure 5).

The ICC between measurements of MWT and IMT (0.347, p<0.001) was statistically significant but lower than the ICC observed for luminal diameter, due to consistently higher values of the MWT compared to IMT (paired sample T-test p<0.001). Furthermore, an upward trend in this difference was observed when wall thickness was increasing [r=0.72 (p<0.001); (figure 3)].

Table 2 | The high correlations with IMT validate the use of these MRI parameters as surrogate markers for atherosclerosis.

Variable	Pearson's coefficient (r)	P-value
MWT vs. IMT	0.84	<0.001
VWA vs. IMT	0.78	<0.001
lumen diameter (MRI vs. US)	0.88	<0.001

IMT=intima media thickness; MWT=mean wall thickness; VWA=vessel wall area.

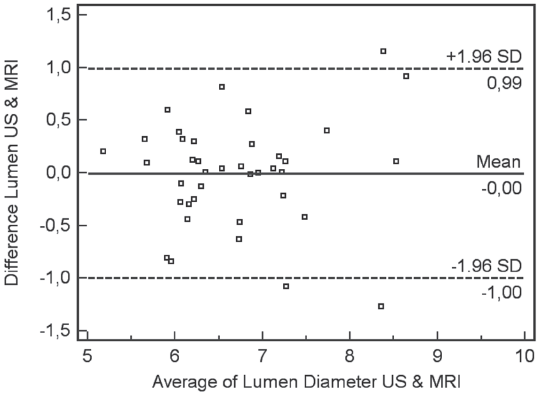

Figure 2 | Bland-Altman plot of ultrasound and MRI values for lumen diameter.

Data indicate a very high agreement between the two imaging modalities, shown by the mean line coinciding exactly with 0.0 and acceptable distribution within a range of 1.96 standard deviations (SD). No trend is seen in the distribution around the mean.

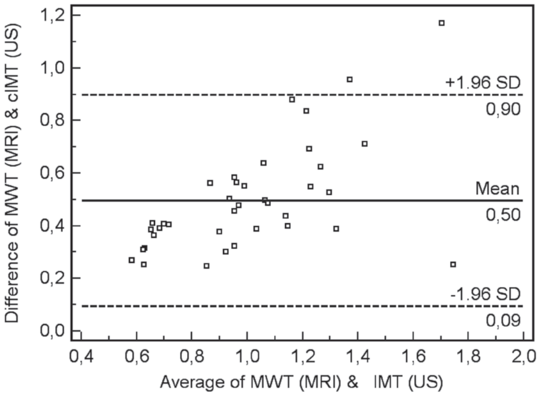

Figure 3 | Bland-Altman plot of ultrasound and MRI values for carotid vessel wall thickness.

Data indicates that MRI findings for MWT are systematically higher than US values of IMT, shown by the mean line coinciding with 0.50. A significant upward trend is seen in the distribution around the mean (r=0.72, p<0.001), implying the difference between US and MRI evaluation is more pronounced with increasing vessel wall thickness.

DISCUSSION

The main findings of the current study are that 3-Tesla MRI measurement of the lumen diameter of the carotid artery almost perfectly agrees with ultrasound measurement, that the MRI measurements of wall thickness and wall area closely correlate with ultrasound IMT measurements, but that MRI systematically finds

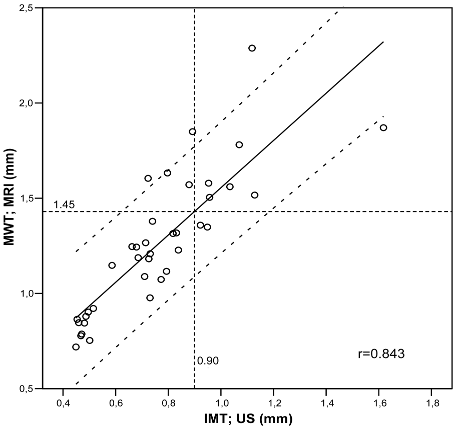

Figure 4 | Scatterplot of mean thickness; IMT (US) vs. MWT (MRI).

Data demonstrate strong correlation between these thickness parameters (r=0.84). The dotted extrapolation lines indicate that the clinically relevant cut-off value of 0.9mm for IMT corresponds with 1.45mm for MWT
IMT=intima media thickness
MWT=mean wall thickness
(———) indicates linear regression line
(- - - -) indicates 95% confidence interval
(------) indicates linear extrapolation lines

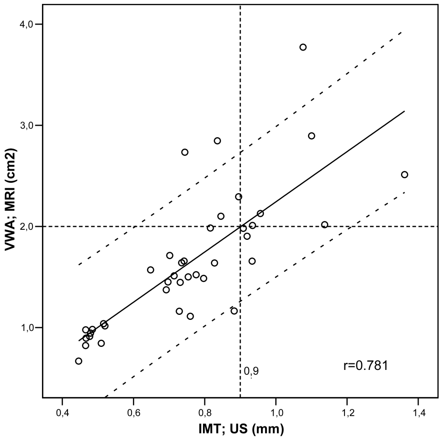

Figure 5 | Scatterplot of IMT (US) vs VWA (MRI).

Data demonstrate strong correlation between the parameters (r=0.78). The dotted extrapolation lines indicate that the clinically relevant cut-off value of 0.9mm for IMT corresponds with 2.00cm^2 for VWA.
IMT=intima media thickness
VWA=vessel wall area.
(———) indicates linear regression line
(- - - -) indicates 95% confidence interval
(------) indicates linear extrapolation lines

higher values for wall thickness than ultrasound. Furthermore, preliminary data are provided to extrapolate IMT cut-off values for higher cardiovascular risk to MRI measurements of wall thickness and wall area.

The high level of agreement in quantifying carotid lumen diameter indicates the dimensional accuracy of MRI as compared to ultrasound. Apparently, the inner vessel boundaries are defined by both techniques adequately without systematic differences allowing very accurate measurements of the lumen diameter.

Previous studies have evaluated the use of black blood fast spin echo MRI at 1.5-Tesla for assessing mean wall thickness of the carotid artery as compared to IMT values. Underhill et al. (25) used a statistical shape modelling technique for automated measurement of mean wall thickness in the common carotid artery by MRI. Patients with a range of carotid artery stenoses were included in that study and not only thin-walled segments as was done in our study. A very high correlation coefficient between MRI measured wall thickness and IMT was reported (r=0.93). In that study 28 out of 43 patients were successfully evaluated by both MRI and ultrasound.

Mani et al. (26) compared MRI based measurements of wall thickness and wall area with IMT in 17 patients with intermediate to high Framingham risk score. In that study a somewhat lower correlation between MRI measurements of mean wall thickness and IMT was reported (r=0.71).

In our study the correlation for measuring wall thickness by MRI and ultrasound is 0.84 and therefor e comparable to the findings in the abovementioned studies. The technical success ratio for completing the MRI study was 95% in our population, higher than reported in previous studies, predominantly done with 1.5Tesla MRI.. It is expected that higher spatial resolution at 3-Tesla may help to better define vessel boundaries and thereby improving accuracy. However, several factors may have contributed to the accuracy of MRI when contrasting the results with those of other studies. The acquisition protocol was different from previously reported protocols. We used a black blood fast gradient echo sequence that has shown good reproducibility in a previous study. (100) Furthermore, we measured relatively thin-walled vascular segments as opposed to stenosed vessels with significant atherosclerosis.

We observed systematically higher MRI-based wall thickness measurements when compared to ultrasound. In addition, we observed a more pronounced difference with increasing wall thickness. This observation has been noted previously (25) (26). Other researchers have provided several explanations for this finding. A factor that contributes to this overestimation is that MRI measurements include the lamina adventitia, whereas ultrasound measures only the combined thickness of the intima and media. Therefore, we speculate that there is increasing adventitial thickening commensurate with overall wall thickening, as is observed in experimental studies. (27) (28) (29) Of note, the degree of overestimation (0.4 mm) is consistent with the thickness of the adventitia and residual media that comprise the artery wall following endarterectomy. Further studies are required to assess the contribution of the adventitia to the wall thickness and to explore its potential clinical significance.

Although the subjects included in the present study were asymptomatic, we observed significant differences in IMT, wall thickness and wall area by MRI when comparing a relative young age group and an older age group. The older group did not exhibit plaque formation. These findings confirm that the carotid artery thickens with advancing age. The data also suggest that it is possible to visualize early stage atherosclerosis by means of MRI, although we cannot make a distinction between physiological vascular adaptation and early atherosclerosis. We have compared the cut-off value of the IMT of 0.9 mm to the MRI measurements of mean wall thickness and wall area. Our preliminary data indicate that the corresponding wall thickness is 1.45 mm and wall area 2.00 cm^2, respectively. Further study is required to assess appropriate threshold values for MRI measurements of wall thickness and wall area as compared to clinically meaningful threshold values by ultrasound.

This study has several limitations. The coverage of the common carotid artery was limited to 1 cm. Further technical improvements by using different acquisition schemes and surface coils may be anticipated to improve spatial resolution. Furthermore, a limited number of subjects of two age groups were included. To assess the clinical relevance of the observations further study is required in larger cohorts with different risk profiles. Moreover, the data for the threshold values for wall thickness and wall area by MRI are only preliminary and have to be explored in follow-up studies with clinical end-points for further validation. Despite these limitations, we believe that our current protocol is optimized for 3-Tesla imaging of the common carotid artery and provides an insight on what can be achieved using this technology.

In conclusion, 3-Tesla imaging of the carotid artery provides excellent dimensional accuracy for measuring the lumen diameter. Close correlations with IMT is achieved for measuring wall thickness and wall area. Further study is required to correlate the MRI findings with different risk profiles to assess the clinical utility for risk stratification and outcomes.

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