Characterization of distensibility, plaque burden, and composition of the atherosclerotic carotid artery using magnetic resonance imaging

Gábor Cantón^{a)}

Mechanical Engineering Department, University of Washington, Box 352600, Stevens Way, Seattle, Washington 98195

Daniel S. Hippe and Jie Sun

Vascular Imaging Laboratory, Department of Radiology, University of Washington, Box 358050, 850 Republican Street, Seattle, Washington 98109

Hunter R. Underhill

Division of Medical Genetics, Department of Medicine, University of Washington, Box 357720, 1959 NE Pacific Street, Seattle, Washington 98195

William S. Kerwin

Vascular Imaging Laboratory, Department of Radiology, University of Washington, Box 358050, 850 Republican Street, Seattle, Washington 98109

Dalin Tang

Mathematical Sciences, Worcester Polytechnic Institute, 100 Institute Road, Worcester, Massachusetts 01609

Chun Yuan

Vascular Imaging Laboratory, Department of Radiology, University of Washington, Box 358050, 850 Republican Street, Seattle, Washington 98109

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Purpose: Arterial distensibility is a marker that can measure vessel wall functional and structural changes resulting from atherosclerosis with applications including estimation of mechanical properties of the wall. We sought to assess the feasibility of using magnetic resonance imaging (MRI) to include wall distensibility in the characterization of atherosclerotic carotid arteries and to analyze the relationship between distensibility and morphological and compositional plaque features.

Methods: Five healthy volunteers were imaged with a multiple-slice CINE MR sequence twice, within 24 h, to determine the interscan reproducibility of distensibility measurements. Twenty-one subjects with >15% carotid stenosis and the five healthy volunteers were imaged using a multicontrast carotid MRI protocol to characterize arterial wall morphology and composition. Normalized wall index (wall area/total vessel area), maximum wall thickness and, if present, percentages of wall area occupied by calcification and lipid-rich necrotic core were determined. A multiple-slice CINE MR sequence was added to the multicontrast protocol to measure the distensibility coefficient (DC) at several locations spanning the bifurcation. The intraclass correlation coefficient (ICC) and the coefficient of variation were used to assess the reproducibility of DC measurements made on the healthy subjects. The DC was compared between arterial segments and between the healthy and diseased groups. Furthermore, within the diseased group, DC was correlated to plaque morphology and composition at each location as well as that averaged over the plaque.

Results: Distensibility measurements were highly reproducible: ICC (95% confidence interval) was 0.998 (0.96–1.0) for the common carotid segment and 0.990 (0.92–1.0) for the internal carotid segment. In healthy volunteers, we found significantly higher distensibility in the common segment of the carotid artery compared to the internal carotid segment (mean $\pm$ SD = 4.56 ± 1.02 versus $3.56 \pm 1.32 \times 10^{-5}$ /Pa; $p < 0.05$). However, no segmental differences were seen in the diseased group (3.25 ± 1.84 versus $3.26 \pm 1.60 \times 10^{-5}$ /Pa; $p = 0.607$). Location-to-location changes in DC were not found to correlate to changes in the local plaque morphology or composition nor were average DC found to be associated with aggregate plaque features.

Conclusions: These results demonstrate the feasibility of MRI to measure distensibility in the carotid artery and to presumably detect changes in distensibility due to age and/or disease. The results suggest that the effect of atherosclerosis on local distensibility may not strongly depend upon the specific underlying plaque features in mild to moderate stenotic carotid lesions though more diffuse or nonlocal changes in arterial distensibility could not be ruled out. © 2012 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4754302>]

Key words: carotid atherosclerosis, distensibility, compliance, MRI

I. INTRODUCTION

An increase in stiffness in the arterial wall leads to an increase in the local pulse pressure. This higher local pulse pressure may lead to structural and functional changes in the vessel wall that trigger an increase in wall thickness, development of atherosclerotic plaques, and eventual plaque rupture.¹ In fact, stiffening of the carotid artery wall has been associated with indicators of atherosclerosis such as common carotid intima-media thickness and presence of plaque in the carotid artery.^{2,3} Moreover, carotid artery stiffness has been shown to predict cardiovascular events, such as ischemic stroke.^{3–6} Although arterial segments affected by atherosclerosis are characterized by marked stiffening,⁷ little is known about the relationship between specific local atherosclerotic plaque features and wall stiffness. In particular, calcification has been shown to be associated with greater wall stiffness,⁸ though, this relationship is not consistent in different arterial segments,^{8,9} and it might refer to medial calcification only, since the association between intimal calcification and arterial stiffness is less definitive.¹⁰

For the carotid arteries, a more thorough understanding of the role of plaque features in determining wall stiffness is being offered by magnetic resonance imaging (MRI). Multicontrast, high resolution MRI is an established imaging tool to identify and quantify the size of components in carotid lesions, as well as plaque burden.^{11–13} In addition, CINE MRI has been proposed as a reliable tool to measure arterial distensibility,¹⁴ an index frequently used to measure stiffness.¹⁵

In this study, we propose to use MRI for a comprehensive evaluation of the carotid atherosclerotic wall by first evaluating its ability to reproducibly measure distensibility and to detect changes between two different populations, young versus diseased and old; and, second, by characterizing subject-specific wall stiffness *in vivo* in healthy and atherosclerotic carotid arteries. We will also evaluate the potential variation of distensibility along carotid bifurcations with atherosclerotic plaques. A standardized multicontrast MRI protocol is applied to characterize vessel wall morphology (plaque burden) and composition; whereas CINE MRI is proposed to measure vessel wall distensibility.

II. METHODS

Twenty-one subjects with carotid stenosis greater than 15% identified by duplex ultrasound and five healthy volunteers were recruited. Four cases were excluded from the diseased group due to failed gating ($n = 3$) and poor image quality ($n = 1$). The age range of the diseased group was 56–87 (male-to-female ratio, 2.5:1), whereas the range of the healthy group was 26–34 (male-to-female ratio, 4:1). The mean systolic and diastolic pressures of the diseased group were 129 ± 22 and 69 ± 10 mm Hg, respectively; and for the healthy group, 116 ± 11 and 73 ± 7 , respectively. More than 60% of the diseased cases had less than 49% stenosis (as measured with ultrasound). Informed consent was obtained prior to sub-

ject participation. The study protocol and consent forms were reviewed and approved by the Institutional Review Board.

II.A. Magnetic resonance imaging data

Subjects' carotid bifurcations were imaged axially using a 3.0 T clinical whole-body scanner (Philips Achieva, Best, The Netherlands) with an eight-channel custom-designed carotid coil.¹⁶ Images were centered at the carotid bifurcation of the index artery, which was defined in the diseased group as the artery with the greatest degree of lumen area reduction as seen on an axial two-dimensional time-of-flight (TOF) MR angiogram (MRA). The left carotid bifurcation was selected as index side for the healthy participants. The imaging protocol included a standardized combination of black and bright blood sequences to characterize the vessel wall morphology and composition with a spatial resolution of $0.55 \times 0.55 \times 2$ mm³.^{17,18} Two experienced readers registered and segmented the images using CASCADE, a custom designed analysis software.¹⁹ Lumen and outer wall boundaries were outlined for each image slice, measuring the resulting lumen, outer wall, and total vessel areas. If detected, lipid-rich necrotic core and calcification boundaries were also outlined following histology-validated imaging criteria¹¹ and their percentage of the wall was computed (%LRNC and %CA, respectively). Plaque burden was characterized in terms of normalized wall index (NWI, defined as the ratio of wall area to total vessel area) and maximum wall thickness (MWT).

The protocol also included a CINE sequence to achieve multiphase (14–30 per heartbeat) imaging with retrospective ECG gating, needed to measure the changes in luminal size that would be used in determining vessel wall stiffness. Two different CINE sequences were used in the diseased group to accommodate participation in a parallel study that began after the first group of participants had been imaged. These CINE sequences consisted of either a phase contrast turbo field echo (TFE) sequence with TR = 16.5 ms, TE = 9.4 ms, and 14 cardiac phases, imaging 5 slices separated by 4 mm gaps (protocol A); or a TFE sequence with TR = 7.1 ms, TE = 4.3 ms, and 30 cardiac phases, imaging 8 slices with 2 mm gaps (protocol B). This change in the CINE parameters was not expected to alter distensibility measurements.

The later protocol (B) was followed when imaging the carotid bifurcation of the healthy group, with the exception that only two slices were imaged: in the CCA at 5 mm proximal to the flow divider and in the ICA at 5 mm distal to the flow divider, to investigate potential differences between the two arterial segments. In all cases, images were acquired in the axial plane with a flip angle of 30°, field of view (FOV) of 160×160 mm², and voxel size of $0.31 \times 0.31 \times 2$ mm³. The healthy volunteers were imaged twice within 24 h to determine the interscan reproducibility of the distensibility measurements.

The luminal boundary of the index side was outlined on all phases using CASCADE, which produced the corresponding luminal area and its change with the cardiac cycle. Maximum and minimum areas were selected as corresponding to

FIG. 1. The registration for the images from the multicontrast [TOF, T1-, T2-, PD-weighted, and magnetization-prepared rapid acquisition gradient-echo (MPRAGE)] and CINE protocols was achieved by using the bifurcation imaged slice (marked 0) as landmark. Note: * denotes lumen of carotid artery and ● denotes lumen of jugular vein.

peak-systolic and end-diastolic areas, respectively. Peak-systolic and end-diastolic diameters were subsequently derived from the areas, assuming perfectly circular luminal shapes. Stiffness was then determined by the distensibility coefficient²⁰

$$DC = \frac{2 \times \Delta D / D_D}{\Delta P},$$

where ΔD is the change in diameter between peak systole and end diastole, D_D is the end-diastolic diameter, and ΔP is the brachial pulse pressure, which was measured before the images were acquired.

Plaque burden, composition, and distensibility were assessed at all imaged slices using the flow divider as a landmark in the registration of the multicontrast and CINE images. Imaged slices were indexed based on their location with respect to this landmark (index 0) as belonging to the common (<0) or the internal (>0) carotid arteries (Fig. 1).

II.B. Statistical analysis

Statistical analysis was performed using R 2.11.0 (R Development Core Team, 2010, R Foundation for Statistical Computing, Vienna, Austria). The DC measurements are summarized as mean $\pm$ SD.

The intraclass correlation coefficient (ICC) and the coefficient of variation (CV) were used to assess the reproducibility of DC measurements made on the healthy subjects. To further assess the feasibility of using MRI for measuring distensibility, the two-sample *t*-test and Fligner variance test were used to detect differences in distensibility between the healthy volunteers and the diseased group.

Slice-level DC measurements were averaged per arterial segment (CCA and ICA) and, separately, per artery. Slice-

level plaque measurements were aggregated similarly except MWT, which was aggregated as the maximum value per segment or artery. Because two different CINE protocols were used in the diseased group, the DC measurements from each protocol were tested for bias using the two-sample *t*-test and for an overall difference in distribution using the Kolmogorov–Smirnov test.

Mean differences between the CCA and ICA were evaluated using the paired *t*-test and correlation between the segments was assessed using Spearman's rank correlation coefficient.

A slice-based analysis was conducted to examine whether changes in local plaque morphology and composition were associated with changes in distensibility at the same location. A linear mixed model with log(DC) as dependent variable was fit for each plaque variable. The linear mixed models were used to account for the correlation between locations within the same subject and the log transform was applied to DC to meet the distributional requirement of the model (Linear and Nonlinear Mixed Effects Models, R package version 3.1-96).²¹ An artery-based analysis was also performed to detect global rather than localized associations between distensibility and plaque morphology and composition using Spearman's rank correlation.

III. RESULTS

III.A. Reproducibility of the distensibility measurements

All ten slices of the common (five healthy volunteers, two scans) and the ten slices of the internal carotid arteries were used to analyze the interscan reproducibility of DC. The ICC [95% confidence interval (CI)] was 0.998 (0.96–1.0) for the

TABLE I. Interscan reproducibility analysis.

	ICC (95% CI)	CV
CCA	0.998 (0.96–1.0)	5.9%
ICA	0.990 (0.92–1.0)	14.0%

Note: CCA = common carotid artery; ICA = internal carotid artery; ICC: intra-class correlation; CI = confidence interval; CV = coefficient of variance.

common carotid segment and 0.990 (0.92–1.0) for the internal carotid segment (Table I).

III.B. Distensibility of diseased and healthy carotid arteries

The DC measurements from protocols A and B were not found to differ on average ($p = 0.613$) or differ in distribution ($p = 0.459$), indicating consistency between protocols. The mean DC values for all subjects are shown in Table II. The healthy carotid bifurcations exhibited a significantly higher DC in the CCA segment compared to the ICA segment (4.56 ± 1.02 vs $3.56 \pm 1.32 \times 10^{-5} \text{ Pa}^{-1}$, $p = 0.025$). In contrast, no significant difference was observed between the 2 segments ($p = 0.607$) in the subset of 12 diseased subjects with imaging coverage of both the internal and common carotid artery. The mean DC value in the diseased arteries ($3.37 \pm 1.45 \times 10^{-5} \text{ Pa}^{-1}$) was lower than that in healthy subjects ($4.06 \pm 1.32 \times 10^{-5} \text{ Pa}^{-1}$), although not significant ($p = 0.298$).

In both healthy and diseased subjects, DC measurements in the ICA and CCA were highly correlated ($r = 0.90$ and 0.78 , respectively). For reference, the DC values computed for all imaged locations and individual diseased subjects are displayed in Fig. 2, indexed by location relative to the flow divider. The DC values were widely distributed and did not show any spatial trend.

III.C. Distensibility and plaque burden/composition

To explore the potential relationship between local plaque features and local distensibility measurements, a slice-based analysis was conducted. The percentage change in average

TABLE II. Distensibility (mean $\pm$ SD $\times 10^{-5}/\text{Pa}$) by vessel segment in 5 healthy and 17 diseased subjects.

	Overall	Common ^a	Internal ^a	p^b	r^c
Healthy	4.06 ± 1.32	4.56 ± 1.02	3.56 ± 1.32	0.025	0.90
Diseased	3.37 ± 1.45	3.52 ± 1.84	3.26 ± 1.60	0.607	0.78
p^d	0.298	0.162	0.703		
p^e	0.466	0.131	0.750		

^aMeasurements from diseased common and internal segments made from 12 subjects with sufficient coverage.

^b p -value comparing common and internal by paired t -test.

^cSpearman's correlation coefficient comparing common and internal.

^d p -value corresponding to the unpaired t -test between diseased and healthy subjects.

^e p -value corresponding to a variance test between diseased and healthy subjects.

FIG. 2. Distensibility (DC) distribution along the carotid bifurcation for the study population. Location indexed as 0 corresponds to the flow divider. The common carotid artery is represented with values lower than 0, whereas the internal carotid artery is represented with values greater than 0.

DC per unit change of each plaque variable was examined (Table III) and we did not detect a significant association between localized changes in plaque morphology or composition and local distensibility.

An artery-based analysis was performed to determine if plaque morphology and composition had a global, rather than localized, impact on wall mechanical properties (Table IV). We did not find any significant correlations between average arterial distensibility and any plaque morphological and compositional characteristics, though the widths of the confidence intervals indicate that the existence of modest correlations cannot be ruled out.

IV. DISCUSSION

There is an increased interest in better determining atherosclerotic plaque vulnerability by performing a comprehensive evaluation of the vessel wall that includes not only wall morphology and composition, but also its mechanical properties and the effect of the hemodynamic forces exerted upon it. Previous studies have already proven MRI to be a powerful tool to characterize human carotid atherosclerotic plaque composition and morphology,^{11,22} including the detection and quantification of plaque features shown to be key determinants of plaque vulnerability.^{23–25} In this study, we proposed to include stiffness, a wall mechanical property, in the evaluation of carotid atherosclerotic lesions with MR

TABLE III. Percent change in slice-measured DC per unit change in plaque variable: Location-based analysis.

	% Δ (95% CI)	p
NWI (per 5% increase)	3.2 (−1.8, 8.4)	0.207
MWT (per 1 mm increase)	2.2 (−6.4, 11.7)	0.620
% LRNC (per 5% increase)	2.3 (−6.6, 12.1)	0.615
% CA (per 5% increase)	−0.3 (−7.1, 7.0)	0.933

Note: CI = confidence interval; NWI = normalized wall index (wall area/total vessel area); MWT = maximum wall thickness; LRNC = lipid rich necrotic core; CA = calcification.

TABLE IV. Correlations of aggregated plaque morphology and composition variables with mean DC.

	r^a (95% CI)	p
Mean NWI	0.07 (−0.52, 0.56)	0.780
MWT	0.03 (−0.52, 0.48)	0.913
Mean% LRNC	−0.23 (−0.66, 0.29)	0.383
Mean% CA	−0.01 (−0.50, 0.48)	0.966

^aSpearman's correlation coefficient. CI: confidence interval; NWI: normalized wall index (wall area/total vessel area); MWT: maximum wall thickness; LRNC: lipid rich necrotic core; CA: calcification.

since carotid arterial stiffness has been associated with the incidence of ischemic stroke.^{6,26} First, we have performed a feasibility analysis by testing the ability of MR to reproducibly measure distensibility in a group of healthy volunteers, and to detect changes due to age and/or disease, comparing distensibility between the healthy group and patients with ultrasound-detected mild to moderate stenosis. Second, we have performed a comprehensive characterization of the atherosclerotic carotid artery wall including plaque burden, composition, and distensibility, a measurement for stiffness. We have also analyzed the potential dependence of distensibility on plaque morphology and composition.

Our results demonstrated the ability of MR to measure distensibility. In the studied population, carotid arteries from healthy subjects become stiffer as they bifurcate from the common into the internal carotid artery. Healthy CCA segments were markedly more distensible than healthy ICA segments. Although the implications of this result are constrained by the small number of volunteers participating in this study, this change in mechanical properties along the bifurcation has also been observed in healthy bifurcations of an older population. Giannattasio *et al.* measured arterial distensibility of the common and internal carotid arteries bilaterally in a group of patients affected by unilateral internal carotid artery stenosis.⁷ Both ipsilateral and contralateral internal carotid arteries were stiffer than their corresponding common carotid arteries. Though we observed this trend in our healthy group, this increase in stiffness as the artery bifurcates was not present in our diseased bifurcations, where both segments showed similar DC values. It is interesting to note that our common carotid segment measurements were performed up to 5 mm below the flow divider; whereas in their study, Giannattasio *et al.* made their measurements 3 cm below the flow divider. Our results seem to suggest that the effect of atherosclerosis on distensibility extends into regions relatively close to the diseased portion of the arterial wall, but not identified as diseased by current imaging criteria. This effect, although still evident, may be less pronounced further upstream,⁷ where the mechanical properties may be different due to the different arterial segment.

Local arterial stiffness of superficial arteries has successfully been determined using ultrasound devices. However, access of the ultrasound probe to the internal carotid segment, and its required orthogonal positioning with respect to the arterial axis for reliable assessment limits the use of ul-

trasound when locally characterizing carotid atherosclerotic plaque stiffness. This limitation can be easily overcome using CINE MR. Indeed, we have shown that CINE images can be used to measure distensibility along the carotid bifurcation of both healthy and diseased individuals. Our results support the suggestion made by Harloff and co-workers that CINE MR is a feasible technique to measure distensibility in patients with carotid atherosclerosis.¹⁴ In their study, they compared carotid wall distensibility measurements obtained from ultrasound and MR in 31 healthy volunteers and 7 carotid atherosclerotic patients. They found a similar, if not smaller, spread of differences in distensibility from the two imaging modalities in the diseased group compared to the healthy group, and a non-significant difference in mean distensibility for the diseased group obtained from the two imaging modalities ($p = 0.13$).

Human and animal studies have shown that plaque contribution to decrease distensibility is not significant until advanced stages of the disease.^{27,28} Changes between 3% and 4.5% in stiffness have been reported only for values of intima-media thickness above 0.8 mm.²⁸ Marked differences in distensibility between human diseased carotid artery and the nondiseased contralateral artery were found, indeed, in a population with more than 75% stenosis.⁷ This might explain the lack of effect of plaque morphology (measured as wall thickness or normalized wall index) on distensibility on our sample population, which presented mild to moderate stenosis.

Mechanical properties of the atherosclerotic arterial wall have been previously measured *ex vivo* by either applying uniaxial tests on strips of diseased arteries and nondiseased controls, or comparing pressure-diameter data from diseased and nondiseased vessels.^{29–31} Although the overall findings were qualitatively similar to this study, the heterogeneous nature of carotid atherosclerotic lesions requires quantifying the specific mechanical properties of the different plaques individually: different wall components contribute to the wall structure and, therefore, stiffness. Reports of *ex vivo* measurements of material properties that included a compositional characterization of the specimens indicated that calcified lesions are stiffer than fibrous ones.²⁹ *In vivo* studies have also shown that carotid distensibility is independently associated with carotid calcification, suggesting that arterial stiffness and arterial calcification are concurrent processes.⁹ We did observe relatively low distensibility in three subjects with highly calcified plaques ($2.3 \pm 0.4 \times 10^{-5} \text{ Pa}^{-1}$ in plaques with more than 9%CA vs $3.6 \pm 1.5 \times 10^{-5} \text{ Pa}^{-1}$ in the remaining plaques, $p = 0.013$). While this finding is more in line with the previous studies of calcification, such highly calcified plaques appear somewhat uncommon. We found no marked difference in distensibility between overall calcified and non-calcified plaques. This disagreement with previous findings might be explained by our smaller sample size but it also supports the suggestion made by Najjar and co-workers³² that age and atherosclerosis might be jointly contributing to distensibility reduction.

There are two limitations in our study that merit discussion. First, the sample size of diseased subjects was limited. However, a *post hoc* power analysis indicates that we had 80% power to detect correlations of 0.63 or greater and 50% power

to detect correlations of 0.46 or greater. Similarly, the 95% confidence intervals for the correlations between distensibility and mean NWI, MWT, and mean% CA (see Table III) indicate that correlations of 0.6 or more would have been detected by our study. Accordingly, the study described herein largely rules out strong associations between distensibility and plaque composition. Nevertheless, future studies would benefit from a larger sample size to study potentially more moderate correlations. And second, brachial artery pulse pressure was utilized instead of carotid artery pulse pressure, which has been reported to lead to an underestimation of distensibility, which may be different for subjects with and without cardiovascular disease.³³

V. CONCLUSION

We have combined multicontrast and CINE MRI protocols to obtain a quantitative comprehensive characterization of the carotid atherosclerotic wall within the same clinical examination. We demonstrated the reliability of MRI to measure distensibility in a group of healthy young volunteers, as well as its ability to differentiate the mechanical properties between that group and an older and diseased group. Distensibility decreased as the common carotid artery bifurcated in healthy individuals, while it was found to be similar between the common and internal carotid arteries in diseased bifurcations, suggesting that the effect of disease on wall mechanical properties affects the whole bifurcation. Further studies measuring the mechanical properties farther upstream from the flow divider should be performed to determine whether this lack of difference in mechanical properties between segments is due to the local effects of the disease or to the older age of this population. In addition, our results suggest that the effect of atherosclerosis on local distensibility may not strongly depend upon the specific underlying plaque features in mild to moderate stenotic carotid lesions though more diffuse or nonlocal changes in arterial distensibility could not be ruled out.

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^{a)} Author to whom correspondence should be addressed. Electronic mail: gcanton@uw.edu; Telephone: (206) 8971315; Fax: (206) 6169354.

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