Correlations between measures of atherosclerosis change using carotid ultrasonography and coronary angiography

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Received 8 February 1999; received in revised form 7 July 1999; accepted 3 September 1999

Abstract

Few studies have examined the correlation between change in carotid artery intima-media thickness (IMT) and change in coronary artery disease. In the Cholesterol Lowering Atherosclerosis Study, current nonsmoking men with coronary artery disease were randomized to colestipol-niacin or placebo. Among 133 subjects with baseline and on-trial coronary angiography and carotid ultrasonography, colestipol-niacin treatment significantly reduced progression of atherosclerosis by both end point measures (2-year average change in percent diameter stenosis by coronary angiography and rate of change in carotid IMT). Significant correlations between change in common carotid artery IMT and quantitative coronary angiographic measures of change were evident over all coronary artery lesions, and in mild:moderate (<50% diameter stenosis), but not severe (>50% diameter stenosis) coronary artery lesions. In mild:moderate lesions, correlations with change in common carotid IMT were: percent diameter stenosis ($r = 0.28, P = 0.002$), minimum lumen diameter ($r = 0.28, P = 0.002$), and vessel edge roughness ($r = 0.25, P = 0.003$). While measures obtained by carotid ultrasonography and coronary angiography are correlated, they each assess different aspects of atherosclerosis change. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Atherosclerosis; Angiography; Ultrasonography; Coronary disease; Carotid arteries

1. Introduction

Assessment of carotid artery intima-media thickness (IMT) by B-mode ultrasound is increasingly utilized as a measure of atherosclerosis, both in epidemiological studies examining the course of atherosclerotic disease and correlations with CHD risk factors [1,2] as well as in clinical trials testing the efficacy of various antiatherosclerosis therapies [3–9]. Determination of carotid artery IMT allows for direct, non-invasive, repeated measurement of early, pre-intrusive atherosclerosis in asymptomatic as well as symptomatic individuals [10].

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The association between carotid IMT and the extent of coronary artery disease has been addressed primarily through cross-sectional analyses. These reports either correlated carotid artery IMT and various measures of coronary artery disease obtained by coronary angiography or compared carotid artery IMT in persons with (typically defined by having a lesion of at least 50% diameter stenosis) and without established coronary artery disease [11–19]. No studies have examined the correlation between serial measures of both carotid artery IMT and coronary artery disease. Few quantitative imaging studies have compared changes in atherosclerosis in one vascular bed with that of another [20].

The Cholesterol Lowering Atherosclerosis Study (CLAS) was a serial arterial imaging clinical trial that tested the efficacy of LDL-lowering in reducing the rate of progression of atherosclerosis in the coronary,
carotid, and femoral arteries [21]. We have previously reported on the treatment benefit of colestipol-niacin on common carotid artery IMT among CLAS subjects and on the correlation of IMT measured in the common carotid artery with visual assessment of coronary artery lesion severity [3,4]. We have also reported that both common carotid IMT rate of change and change in coronary artery disease assessed by quantitative coronary angiography (QCA) are significantly predictive of clinical coronary events among the CLAS cohort [22,23]. We now report on the association between common carotid artery IMT measured by automated computerized edge tracking and various angiographic measures of coronary artery disease determined by QCA. We examined these associations at a single time point (at baseline) as well as serially (change in end point measures).

2. Methods

2.1. CLAS study design

CLAS was a randomized, double-blind, placebo-controlled serial arterial imaging clinical trial testing the efficacy of LDL-cholesterol lowering in reducing the rate of progression of atherosclerosis. Subjects were 188 non-smoking males, 40–59 years old, with prior coronary artery bypass graft surgery who were randomized to colestipol-niacin or placebo [21]. All subjects provided written informed consent for participation in the trial, which was approved and monitored by the university IRB.

2.2. Coronary angiography and study end points

Coronary angiograms were obtained at baseline and 2 years using the percutaneous femoral technique with sufficient right and left anterior oblique views to clearly visualize all coronary artery lesions. After completion of the 2-year angiogram, quantitative coronary angiography (QCA) was performed blinded to treatment group assignment. A panel of expert angiographers identified the coronary artery lesions prior to evaluation by the QCA technician. Film pairs were processed in tandem with dual projectors to match frames for orientation and degree of contrast filling.

For all coronary artery lesions evaluable by QCA, percent diameter stenosis and minimum lumen diameter were measured. For all evaluable coronary artery segments, defined from branch to branch, the percent diameter stenosis, minimum lumen diameter, average diameter, and vessel edge roughness were computed. The vessel edge roughness for a coronary artery segment was defined as the root mean squared deviation of the measured vessel edge from a straight line fit through the segment vessel edge profile. Three sequential frames exposed during end-diastole were digitized when possible; otherwise three sequential frames from other phases of the cardiac cycle were used. The QCA measures were averaged over the three frames for each lesion or segment evaluated [24] and were obtained in all evaluable native coronary arteries. For each subject, summary QCA measures were computed by averaging over all measured lesions or segments.

Other measures of change in coronary artery atherosclerosis which might be considered more clinically relevant were determined from the QCA data. A new lesion was defined as a lesion that was not identified on the baseline angiogram, but was at least 20% diameter stenosis on the 2-year angiogram. A progressing lesion was defined as a lesion of at least 20% diameter stenosis on the baseline angiogram, which had showed an increase of at least 12% diameter stenosis on the 2-year angiogram. In a reproducibility study of measures obtained by our QCA methodology, 17 patients (measuring 49 coronary artery segments and 55 coronary artery lesions) received two angiograms during the same examination, with repositioning between the two angiograms [25]. The standard deviation of the difference in lesion percent diameter stenosis, an estimate of the inherent measurement error, was 6%. We therefore chose twice this standard deviation as a cutoff for defining ‘true’ progression (or regression) of coronary artery lesions (i.e. lesion change beyond that expected only by measurement error). A regressing lesion was defined as a lesion of at least 20% diameter stenosis at baseline, which had decreased by at least 12% diameter stenosis at 2 years. A new total occlusion was an occluded vessel at 2 years, which was not occluded at baseline. The number of each of these QCA-derived measures was computed for each subject. The number of changing lesions for each subject was computed as the difference between the number of progressing and regressing lesions.

2.3. Carotid ultrasonography and measurement of common carotid IMT

Subjects were scanned with a Biodynamics Biosound ultrasound system using a 9-MHz probe. Carotid artery ultrasounds were performed prior to randomization and during the trial.

Ultrasound images were analyzed at end diastole with a Northgate 386/33-computer system equipped with a Data Translation DT 2862 digitizing and image processing board. The process of digitizing the ultrasound image, tracking the lumen-intima and media-adventitia echoes, and computing IMT by automated edge detection (PROSOUND software) has been previously described [26]. In brief, the lumen-intima and media-adventitia echoes are located with an edge track-
ing algorithm in which: (1) an initial echo boundary is identified with a mouse; (2) this initial boundary is used to guide an edge-finding algorithm to locate a conditional set of edges, and (3) these conditional edges are tested for ‘edge strength’ and weak edges are eliminated. Using all acceptable edge pairs (lumen-intima to media-adventitia), the IMT is then computed as the average separation between the two edges.

An operator who selected one end-diastolic frame analyzed videotapes from a 5 to 10-s recording using maximum lumen-intima continuity and echo brightness as selection criteria. Average IMT was computed over a 1 cm length of the far wall of the common carotid artery ending approximately 1/2 centimeter proximal to the transition between the common and bulb regions. For all subjects, care was taken to match the longitudinal position of the analyzed segment on serial images.

In a short-term reproducibility study of our ultrasound and IMT measurement methodology, eight subjects were scanned twice (1 week apart) by three ultrasonographers [26]. The inter-sonographer standard deviation of carotid artery IMT was 0.026 mm for ultrasonographers [26]. The inter-sonographer standard deviation was 0.016 mm for replicate scans performed on the same day. The intra-sonographer standard deviation was 0.029 mm for replicate scans obtained 1 week apart.

2.4. Statistical analysis

QCA variables selected for analysis were considered standard angiographic measures of extent and change in coronary artery disease by virtue of their prior use as end points in coronary angiographic trials. Because of the different progression rates observed in native coronary arteries as compared with coronary artery bypass grafts [27], each QCA measure was evaluated over native artery lesions/segments only. Analyses were also limited to native artery lesions/segments that were hemodynamically unrelated to bypass grafts; these analyses included only lesions or segments in vessels that had not been bypassed. In addition, because the predictability of coronary events by change in coronary artery disease is related to initial lesion severity [22], each QCA measure was evaluated according to two categories of baseline severity: < 50% diameter stenosis (mild/moderate) and ≥ 50% diameter stenosis (severe). Both baseline and on-trial changes (2-year minus baseline) for these QCA measures were analyzed. Analyses of changes in coronary artery disease also included the QCA-derived measures of numbers of new lesions, progressing lesions, regressing lesions, changing lesions, and new total occlusions.

Two carotid IMT measures were analyzed: baseline IMT and rate of change over the 2-year study period. The IMT change rate was estimated by regressing each subject’s IMT data on time since randomization; the resulting slope estimate was used as the subject’s IMT change rate (in mm/year).

Associations between QCA and IMT variables were evaluated using correlational analyses. Nonparametric Spearman rank correlations were used for all analyses because of the non-normal distributions of some of the QCA variables. To estimate the degree of association at a single point in time, baseline variables were analyzed using the entire sample (combined treatment groups). Associations between coronary angiographic versus carotid IMT changes were also estimated by correlating QCA and IMT change variables in a combined analysis. To further evaluate the common carotid IMT change rate as an indicator of atherosclerosis change relative to QCA end point measures, simple correlations of on-trial lipids were correlated with the common carotid IMT change rate and the average change in percent diameter stenosis of coronary artery lesions. Finally, the effect of randomized treatment on each atherosclerosis outcome measure (common carotid IMT change rate and change in percent diameter stenosis of coronary artery lesions) was analyzed using t-tests for independent samples.

3. Results

3.1. Sample characteristics and treatment effects

Of the 188 subjects randomized, 19 (10%) had neither an ultrasound or QCA end point, 23 (12%) had a QCA but no ultrasound end point, and 13 (7%) had an ultrasound but no QCA end point. The sample for analysis was composed of 133 subjects who had both baseline/2-year coronary angiograms evaluated by QCA and baseline and follow-up carotid ultrasonography (Table 1). Subjects were primarily middle-aged

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline sample characteristics (n = 133)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) or % (n)</td>
</tr>
<tr>
<td>Age at randomization</td>
<td>54.1 (4.5)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.3 (0.9)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.1 (0.2)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>4.4 (0.8)</td>
</tr>
<tr>
<td>Total triglycerides (mmol/l)</td>
<td>1.7 (1.0)</td>
</tr>
<tr>
<td>Apolipoprotein A-I (mg/dl)</td>
<td>118.6 (18.4)</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dl)</td>
<td>125.5 (27.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121.4 (12.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.6 (8.6)</td>
</tr>
<tr>
<td>Ex-smokera</td>
<td>71% (94)</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>50% (67)</td>
</tr>
<tr>
<td>Placebo</td>
<td>50% (66)</td>
</tr>
</tbody>
</table>

a The CLAS design required all subjects to be current non-smokers; thus all smokers were ex-smokers at the time of the study.
males who were on average normotensive with moderate hypercholesterolemia; 71% were ex-smokers. QCA measures were computed on an average of 5.7 native coronary artery lesions and 7.7 native coronary artery segments (defined from branch to branch) per subject. Carotid IMT was obtained from an average of 2.8 serial ultrasonograms per subject, with an average duration of 2 years from first to last carotid ultrasound. These 133 subjects did not differ from the 55 subjects not included in this analysis on age, years since bypass, smoking history, randomized treatment group, or baseline and on-trial levels of blood pressure, total cholesterol, HDL-cholesterol, LDL-cholesterol, and total triglycerides (data not shown).

Among these 133 subjects with both coronary angiographic and carotid IMT end point measures, the treatment effect on change in coronary artery lesion percent diameter stenosis was statistically significant (mean (SEM) change in colestipol–niacin group = 0.39 (0.75) percent diameter stenosis, in placebo group = 2.87 (0.71) percent diameter stenosis, \( P = 0.02 \)). The treatment effect on common carotid IMT change rate was also statistically significant (mean (SEM) IMT change rate = \(-0.024 (0.004) \text{ mm/year} \) in the colestipol–niacin group, and \( 0.020 (0.003) \text{ mm/year} \) in the placebo group, \( P < 0.0001 \)). Treatment effect sizes (difference in treatment group means, divided by the pooled standard deviation) were 0.42 for change in percent diameter stenosis, and 1.62 for the IMT change rate.

### 3.2. Correlations between common carotid artery IMT and QCA measures at baseline

Table 2 provides the Spearman correlations between a single baseline carotid IMT measure and QCA measures obtained from the baseline coronary angiogram.

<table>
<thead>
<tr>
<th>QCA measure</th>
<th>Correlation (95% CI) of baseline QCA measure with baseline carotid IMT (mm)</th>
<th>Correlation (95% CI) of QCA change measure with carotid IMT change rate (mm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percent diameter stenosis (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All native lesions ((n = 129))</td>
<td>(-0.04 , (-0.22, 0.14))</td>
<td>(0.21 , (0.04, 0.38)) §</td>
</tr>
<tr>
<td>Native lesions &lt;50% ((n = 125))</td>
<td>(0.01 , (-0.17, 0.19))</td>
<td>(0.28 , (0.10, 0.43)) §</td>
</tr>
<tr>
<td>Native lesions (\geq 50% ((n = 93))</td>
<td>(-0.03 , (-0.23, 0.19))</td>
<td>(0.00 , (-0.21, 0.21))</td>
</tr>
<tr>
<td>Unrelated native lesions ((n = 93))</td>
<td>(-0.03 , (-0.24, 0.18))</td>
<td>(0.33 , (0.13, 0.50)) ¶</td>
</tr>
<tr>
<td>All native segments ((n = 133))</td>
<td>(0.16 , (-0.01, 0.33))</td>
<td>(0.28 , (0.11, 0.44)) §</td>
</tr>
<tr>
<td>Native segments &lt;50% ((n = 133))</td>
<td>(0.14 , (-0.04, 0.31))</td>
<td>(0.30 , (0.13, 0.45)) §</td>
</tr>
<tr>
<td>Native segments (\geq 50% ((n = 85))</td>
<td>(-0.08 , (-0.30, 0.14))</td>
<td>(0.07 , (-0.15, 0.28))</td>
</tr>
<tr>
<td>Unrelated native segments ((n = 107))</td>
<td>(0.03 , (-0.16, 0.23))</td>
<td>(0.25 , (0.06, 0.42)) §</td>
</tr>
</tbody>
</table>

**Minimum lumen diameter**

| All native lesions \((n = 129)\) | \(-0.03 \, (-0.21, 0.14)\) | \(-0.22 \, (-0.38, -0.04)\) § |
| Native lesions <50% \((n = 125)\) | \(-0.07 \, (-0.25, 0.11)\) | \(-0.28 \, (-0.44, -0.11)\) § |
| Native lesions \(\geq 50\% \((n = 93)\) | \(-0.02 \, (-0.22, 0.20)\) | \(0.01 \, (-0.20, 0.22)\) |
| Unrelated native lesions \((n = 93)\) | \(0.04 \, (-0.17, 0.25)\) | \(-0.20 \, (-0.40, 0.01)\) ¶ |
| All native segments \((n = 133)\) | \(-0.09 \, (-0.26, 0.08)\) | \(-0.15 \, (-0.32, 0.02)\) |
| Native segments <50% \((n = 133)\) | \(-0.07 \, (-0.25, 0.10)\) | \(-0.17 \, (-0.34, 0.00)\) ¶ |
| Native segments \(\geq 50\% \((n = 84)\) | \(0.06 \, (-0.16, 0.27)\) | \(-0.03 \, (-0.25, 0.20)\) |
| Unrelated native segments \((n = 107)\) | \(0.12 \, (-0.08, 0.31)\) | \(-0.08 \, (-0.27, 0.12)\) |

**Vessel edge roughness**

| All native segments \((n = 133)\) | \(0.10 \, (-0.08, 0.27)\) | \(0.20 \, (0.02, 0.36)\) § |
| Native segments <50% \((n = 133)\) | \(0.17 \, (0.00, 0.34)\) | \(0.25 \, (0.08, 0.41)\) § |
| Native segments \(\geq 50\% \((n = 84)\) | \(-0.10 \, (-0.31, 0.12)\) | \(-0.07 \, (-0.29, 0.15)\) |
| Unrelated native segments \((n = 107)\) | \(0.17 \, (-0.02, 0.36)\) | \(0.25 \, (0.06, 0.43)\) § |

**Average segment diameter**

| All native segments \((n = 133)\) | \(-0.04 \, (-0.22, 0.13)\) | \(0.01 \, (-0.17, 0.18)\) |
| Native segments <50% \((n = 133)\) | \(-0.05 \, (-0.23, 0.12)\) | \(-0.01 \, (-0.18, 0.17)\) |
| Native segments \(\geq 50\% \((n = 84)\) | \(0.03 \, (-0.19, 0.25)\) | \(0.05 \, (-0.17, 0.27)\) |
| Unrelated native segments \((n = 107)\) | \(0.12 \, (-0.08, 0.31)\) | \(0.13 \, (-0.07, 0.31)\) |

* Each QCA measure represents the value (baseline or 2-year change) averaged over all evaluable lesions/segments in native coronary arteries.
* 95% CI = 95% confidence interval.
* Analysis includes only native lesions/segments hemodynamically unrelated to bypass graft (lesion-based analyses \(n = 93\) subjects; segment-based analyses \(n = 107\) subjects).
* \( P < 0.05 \).
* \( P < 0.01 \).
* \( P < 0.001 \).
QCA measures represented in Table 2 were obtained from lesions/segments in native arteries only. Except for a positive correlation with the average vessel edge roughness in native coronary artery segments of less than 50% diameter stenosis, there were no significant correlations between common carotid IMT and baseline QCA measures. Results were similar when analyses were conducted on all native lesions (or segments) or limited to native lesions (segments) hemodynamically unrelated to bypass grafts. Correlations of common carotid IMT at baseline with numbers of coronary artery lesions evident at baseline (at least 20% diameter stenosis) were: all native coronary artery lesions \((r = 0.11)\); severe native coronary artery lesions of at least 50% diameter stenosis \((r = 0.02)\); mild/moderate native coronary artery lesions of 50% diameter stenosis or less \((r = 0.15)\) (all correlations not significantly different from zero).

### 3.3. Correlations between serial measures of common carotid artery IMT and QCA

QCA measures of change in coronary artery disease were correlated with the rate of change of common carotid IMT (slope of IMT versus time; Table 2). These correlations were evident when assessed in all native lesions, in native lesions hemodynamically unrelated to bypass grafts, and in mild/moderate lesions. QCA measures assessing change in severe lesions \((\geq 50\%\) diameter stenosis) were not related to the rate of change of carotid IMT. The associations reached statistical significance for QCA measures of percent diameter stenosis (measured both over coronary artery lesions and segments), minimum lumen diameter \((\text{MLD})\) in lesions and segments), and vessel edge roughness. Change in vessel edge roughness was positively correlated with common carotid IMT rate of change, with the correlation most evident in mild/moderate lesions in native vessels \((r = 0.25, P = 0.003)\). In contrast to these measures of change in coronary artery disease, the change in the average lumen diameter (averaged over all coronary artery segments) was not correlated with the carotid IMT rate of change.

### 3.4. Correlations between serial measures of common carotid artery IMT and QCA derived measures

The common carotid IMT change rate was not correlated to the number of new coronary artery lesions \((r = 0.02, 95\%\ CI = -0.15, 0.20)\) or new total occlusions of the native coronary arteries \((r = 0.04, 95\%\ CI = -0.13, 0.21)\). Carotid IMT change was non-significantly correlated with the number of progressing \((r = 0.17, 95\%\ CI = -0.01, 0.33)\) and regressing \((r = -0.15, 95\%\ CI = -0.32, 0.03)\) native coronary artery lesions. The summary variable of total number of changing lesions, which was the number of progressing lesions minus the number of regressing lesions, was positively and significantly correlated with the common carotid IMT change rate \((r = 0.24, 95\%\ CI = 0.07, 0.40, P = 0.005)\).

### 3.5. Associations between common carotid IMT, QCA, and lipids

Correlations between the average lipid levels measured on-trial with the common carotid IMT change rate and change in percent diameter stenosis of coronary artery lesions are displayed in Table 3. For each lipid, the row displays the simple (unadjusted) correlation with change in carotid IMT (or coronary artery percent diameter stenosis). All correlations are in the expected direction and are statistically significant. Simple correlations of on-trial lipids with change in coronary artery lesions ranged from 0.19 (triglycerides) to 0.29 (LDL-cholesterol). Lipid correlations with the common carotid IMT change rate ranged from 0.18 (triglycerides) to 0.44 (LDL-cholesterol).

### 4. Discussion

Data from CLAS indicate that, over a 2-year study period, the rate of change of common carotid artery IMT as a noninvasive measure of early preinvasive atherosclerosis is positively correlated with changes in coronary artery atherosclerosis determined by a variety of QCA measures. The relationships with common carotid artery IMT rate of change were most apparent in mild/moderate, but not severe coronary artery lesions. Previous studies evaluating a single measure of IMT have shown that carotid artery IMT is higher on average in hypertensive compared to normotensive sub-
neither atherosclerosis nor progression of lesions of less than 50% diameter stenosis do not represent normal coronary disease. It is now well recognized that lesions of less than 50% diameter stenosis were considered to have no coronary artery disease. In other words, in these cross-sectional analyses to the broader analyses using all native coronary arteries (Table 2).

Except for coronary vessel edge roughness, we found no correlation between baseline QCA measures and common carotid artery IMT. These results are in contrast to previous reports, which have shown associations between cross-sectional measures of carotid artery IMT and percent diameter stenosis used as a coronary angiographic measure of atherosclerosis [11–19]. While the majority of previous studies have used more global visual measures of extent of coronary artery disease, such as the number of diseased vessels, only one study has previously used QCA measures of lesion severity and segment size [19].

Inclusion criteria for the CLAS study limited subjects to those with coronary artery disease severe enough to warrant bypass graft surgery. The resulting reduction in variability in coronary artery disease relative to a population of subjects presenting for coronary angiography was a possible factor in reducing the observed correlations between baseline measures of coronary artery disease and carotid artery IMT. Previous cross-sectional correlation studies have included subjects who had undergone coronary angiography for clinical indications [11–19]. The resulting samples included persons with coronary artery disease (with angiographic evidence of a coronary artery lesion of a pre-defined severity) and without coronary artery disease (subjects with lesions less than the pre-defined severity). Although these studies were therefore more likely than the present study to detect cross-sectional associations between coronary artery disease and carotid artery disease. In other words, in these cross-sectional and case-control studies that used such a definition, individuals with lesions of less than 50% diameter stenosis were considered to have no coronary artery disease (‘normal’ angiograms), and were used as the comparison group with subjects with more severe lesions. It is now well recognized that lesions of less than 50% diameter stenosis do not represent normal coronary anatomy. To the contrary, progression of this class of lesions is most closely related to the risk of clinical coronary events [22].

The present report from CLAS is one of only a few to evaluate the relationship between change in atherosclerosis, determined by IMT in the carotid artery and by QCA in the coronary arteries. In contrast to our current findings, a clinical trial of pravastatin reported no significant correlations between the change in carotid IMT and QCA measures of change in percent diameter stenosis, change in average lumen diameter, and change in minimum lumen diameter [31]. All QCA measures were obtained over all evaluable coronary artery segments, without regard to severity of disease of the segment. Comparison of results of these two studies is hampered by the fact that the prior study did not report the correlation coefficients [31]. However, in CLAS, QCA change measures evaluated over all coronary segments showed lower correlations with rate of change of common carotid artery IMT than QCA change measures evaluated over segments with lesions (Table 2). In addition, significant correlations were noted only in lesions of mild/moderate severity and not in severe lesions of greater than 50% diameter stenosis.

The correlations between the rate of change of common carotid artery IMT and QCA measures of coronary artery atherosclerosis change ranged from 0.17 to 0.33. These correlations are of a comparable magnitude to those reported with cross-sectional data between the carotid and coronary arteries and within carotid artery sites. Representative of the several studies using visual assessment of coronary artery disease [11–18], a correlation of 0.34 was reported between a summary measure of maximal IMT over several carotid artery sites and the presence of a coronary artery lesion of at least 50% diameter stenosis [32]. Studies evaluating changes in carotid artery lesions, rather than IMT, in relation to progression of coronary artery disease have found larger correlations of around 0.41 [20]. In addition, the histological age-adjusted correlations between carotid and coronary artery atherosclerosis in a large autopsy study ranged from 0.29 to 0.36 [33]. In agreement with these histological correlations was our finding that common carotid artery and coronary artery vessel edge roughness were significantly correlated ($r = 0.25$), since computer measures of angiographic edge roughness correlate significantly with vessel wall cholesterol content ($r = 0.70, P < 0.001$) [34]. Further, a previous report from the CLAS study demonstrated that carotid artery IMT is significantly correlated with carotid angiographic vessel edge roughness ($r = 0.31, P < 0.05$) [3]. It is also notable that the magnitude of the correlations between common carotid artery IMT and QCA measures of coronary artery atherosclerosis change reported here are completely within the range of correlations observed in CLAS for lipid and lipoprotein risk factors and coronary artery atherosclerosis (Table 3).
Using data from the same CLAS cohort, we have reported that the rate of change of IMT in the common carotid artery is significantly associated with the risk of incident clinical coronary events over a 10-year follow-up period [23]. In several epidemiologic studies, a single measure of carotid IMT was related to the risk of subsequent cardiovascular events (including fatal and nonfatal myocardial infarction and stroke) among male and female subjects free of cardiovascular disease at their IMT measurement [35–38]. In the CLAS cohort, for each 0.03 mm increase per year in common carotid artery IMT, the relative risk (RR) for nonfatal MI or coronary death was 2.2 (95% CI = 1.4, 3.6), and the RR for nonfatal MI, coronary death, or coronary artery revascularization was 3.1 (95% CI = 2.1, 4.5) [23]. In the same post-trial follow-up of CLAS subjects using QCA measures of percent diameter stenosis and minimum lumen diameter, changes in mild/moderate lesions (<50% diameter stenosis), but not severe lesions (≥50% diameter stenosis), was predictive of subsequent clinical coronary events [22]. These results are of particular interest given our current finding that the correlation between changes in common carotid IMT and coronary artery disease is most pronounced with progression of mild/moderate lesions, the very lesions predictive of clinical coronary events. Current understanding is that mild/moderate lesions lead to clinical coronary events through plaque rupture with sudden vascular occlusion [39].

When considered multivariately, both carotid IMT rate of change and QCA change in percent diameter stenosis were independently associated with the risk of coronary events [23]. The positive but weak correlations between change in common carotid artery IMT and coronary angiographic measures of atherosclerosis also suggest that the two methods, while capturing certain common aspects of the atherosclerotic process, separately reflect unique aspects of atherosclerosis progression. While visualization and quantification of the intima-media complex has been proposed to be a measure of vessel wall changes early in the atherosclerotic process [10], coronary angiography can only indirectly measure the degree of atherosclerosis by assessing residual lumen size. Coronary angiography can therefore only quantify atherosclerosis at the relatively later stage of intrusive lesion formation. This is consistent with observations of higher correlations between angiographic measures of coronary artery disease and carotid artery lesions as compared to carotid artery IMT [20]. In conjunction with the greater precision and reliability of IMT measures compared to QCA measures, it also explains why the carotid IMT change rate was a more sensitive measure of the effect of colestipol–niacin treatment (treatment effect size = 1.62) than was change in percent diameter stenosis (treatment effect size = 0.42). Taken together, these data indicate that common carotid artery IMT incorporates additional, independent information on prediction of coronary events beyond the angiographic measurement of lumen narrowing. This is perhaps illustrated by the relationship between common carotid artery IMT and coronary vessel edge roughness which may represent atherosclerotic burden and the propensity for plaque rupture and clinical coronary events. These results suggest that use of both IMT and QCA change end points may be particularly useful multiple end points for clinical trials of anti-atherosclerosis interventions with the ultimate goal of reducing coronary event risk. This is of particular importance since the ability to solely use coronary angiographic end points to test anti-atherosclerosis therapies has become a great challenge with the current use of aggressive mechanical intervention for cardiac symptoms. Intervening revascularization procedures have profound effects on follow-up coronary angiograms, and in most cases render the follow-up angiographic data useless as a comparison to a pre-intervention angiogram. Even the effects of coronary angioplasty, once thought to be limited to the intervened coronary artery segment, may effect remote vessel segments through vascular remodeling, thereby altering the true angiographic effects of an anti-atherosclerosis medical therapy [40].

Higher correlations with measures of coronary artery disease have been noted for IMT measured in the carotid bulb compared to common carotid artery IMT [19]. Since atherosclerosis in the carotid arteries generally develops at the bifurcation well before the common carotid artery, a greater progression of IMT at the bifurcation would be expected to more highly correlate with disease in the coronary arteries. However, for research and clinical purposes, distinct advantages of common carotid IMT over IMT measured at the carotid artery bifurcation lie in its greater reproducibility and ability to more consistently visualize the intima-media complex on ultrasound.

In conclusion, our results indicate that the noninvasive measurement of rate of change of the common carotid IMT by ultrasonography is positively correlated with the change in coronary artery atherosclerosis determined by angiography. Our results also suggest that while measures obtained by the two arterial imaging methods are correlated, they also each assess different aspects of atherosclerosis, and thus may be useful as multiple end point measures in clinical trials.

Acknowledgements

This work was supported by NIH grant numbers RO1-HL49885 and RO3-HL54532.
References


