Prevalence and Predictors of Carotid Wall Triple Line Pattern in a General Population Sample

Andrew Ryabikov, Sofia Malyutina, Julian Halcox, Yuri Nikitin, Michael Marmot, Martin Bobak

Objective—Carotid intima-media thickness (IMT) and plaques are markers of atherosclerosis and predict cardiovascular events. A specific triple line pattern (TLP) in the sonograph of the carotid wall has been identified in different conditions, but its origin and clinical significance are unclear. We examined the prevalence and predictors of TLP in a general population.

Methods and Results—The study was conducted in random sample of the general population of Novosibirsk, Russia, within the international Health, Alcohol and Psychosocial Factors in Eastern Europe project. In a subsample of 418 men (aged 45 to 69), carotid IMT, the presence of atherosclerotic plaques, and the presence of TLP were assessed by ultrasound. The prevalence of TLP was 21%. It was associated with IMT (odds ratio = 9.53 per 1 SD, P < 0.001) and the presence of plaques (odds ratio = 2.42, P = 0.002). Other predictors of TLP in multivariate models included age, systolic blood pressure, total cholesterol, and smoking. In addition, infrequent consumption of high amounts of alcohol approximately doubled the risk of triple pattern.

Conclusion—Our findings showed high prevalence of TLP of carotid wall in a general male population sample from a typical Russian city. This sonographic pattern was strongly associated with cardiovascular risk factors and diseases, bioimaging indicators of atherosclerosis, and episodic heavy drinking. (Arterioscler Thromb Vasc Biol. 2011;31:00-00.)

Key Words: alcohol ▪ carotid arteries ▪ Doppler ultrasound ▪ risk factors ▪ intima-media thickness

Ultrasound measures of carotid intima-media thickness (IMT)1–3 and atherosclerotic plaques4 are recognized markers of atherosclerosis and predictors of cardiovascular events. More recently, atypical sonographic patterns of carotid intima-media layering have been identified in patients with different conditions: localized gray-level inhomogeneity of intima-media in patients with coronary heart disease and in older subjects5; alteration of the typical carotid intima-media composition with additional layer in diabetic patients6; fibromuscular renal dysplasia7 and carotid Takayasu arteritis.8 This phenomenon is also referred to as triple signal or triple line pattern (TLP) of arterial wall, to distinguish from the typical double line pattern.9,10 Given the various conditions in which it has been observed, its origin and relationship with atherosclerosis are unclear. To our knowledge, it has not been systematically investigated in unselected populations to define the prevalence, possible causes, and clinical significance.

We used data from a population survey in Russia to examine (1) the prevalence of the TLP of carotid wall in a general population sample, (2) the relationship of TLP with carotid IMT and presence of plaques, and (3) the predictors of this phenomenon. We assessed the associations of TLP with risk factors linked with IMT in previous studies1,2,11–13; in addition, given major concerns regarding the effects of heavy alcohol intake on cardiovascular diseases in Russia,14–16 we have examined a number of measures of alcohol consumption.

Methods

Study Population

The subjects were enrolled in the Health, Alcohol and Psychosocial Factors in Eastern Europe project, a large population-based study in 4 eastern European countries.17 In Novosibirsk, Russia, 9363 men and women 45 to 69 years old participated in the study (response rate 61%). A random subsample of men attended ultrasonographic examination (n = 418, 98.5% of invited). The Ethics Committee at the Institute of Internal Medicine approved the study, which was conducted according the principles of the Helsinki declaration. All participants gave written informed consent.

Data Collection

The structured questionnaire covered medical history, medication, health behaviors, cardiovascular risk factors, and socioeconomic circumstances. The mean of 3 blood pressure (BP) readings was used in the analysis. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Participants provided a blood sample. The serum concentration of total and high-density lipoprotein (HDL) cholesterol, triglycerides, and blood glucose were
Ultrasonographic Evaluation of Carotid Arteries

Carotid arteries were imaged and analyzed by an experienced physician (A.R.) who was blinded to the participants’ characteristics. All studies were performed using the SIM 7000CFM ultrasound system (ESAOTE Spa, Florence, Italy) with 7.5/10-MHz phased-array transducer. Device settings were adjusted in accordance with ASE recommendations.20 First, longitudinal and transversal scans were performed at the right and left common carotid arteries (CCA), with branches to assess the anatomy and atherosclerotic lesions. The plaque was defined in accordance with the Manheim consensus.21 Third, the divergence from the normal ultrasound morphology of CCA wall, as represented by double line layering,9,10 was assessed. We focused on the presence of a TLP.7 The TLP was characterized by an additional discernable reflection line in intima-media compartment of the far wall, it was defined in plaque-free area, and it was continuous and expanded through the transducer’s window in longitudinal view (Figure). The gain setting was adjusted to avoid intraluminal scatter echoes. To reduce likelihood of artifacts mimicking TLP, we insonated arteries by altering probe position on the neck, and varying the depth, focus settings, and the frequency and angle of interrogation. The Figure shows the images of typical double line structure of CCA wall (A) and TLP (B and C). Arrows show additional interface in intima-media projection.

Results

General Characteristics of the Sample Studied

Characteristics of the sample are shown in Table 1. Carotid plaques were identified in more than half of these middle-aged men. The mean IMT was 0.72 mm, and 11% had increased IMT (≥0.9 mm). One fifth of the sample had the TLP of CCA wall. Table 1 shows the age-adjusted comparison of participants’ characteristics. Those with TLP had a greater CCA IMT and higher prevalence of carotid plaques. Those with TLP were older; had higher systolic BP, BMI, total cholesterol (TC), HDL cholesterol, glucose, antihypertensive treatment, smoking, and alcohol drinking, the odds of TLP were more than 9-fold for each 1 SD of alcohol intake, frequency of binge drinking, and the largest amount of alcohol on single occasion.15,16

Statistical Analysis

First, we estimated the prevalence of TLP and the differences in means and proportions of covariates between persons with and without the triple pattern (crude and age-adjusted). Second, the relationship between TLP and established markers of carotid atherosclerosis was estimated using ANOVA for continuously measured IMT and logistic regression for the binary measure of presence of plaques. Third, we investigated the associations between TLP and covariates using logistic regression. The selected independent variables included age, systolic BP, BMI, total cholesterol (TC), HDL cholesterol, blood glucose, smoking, alcohol drinking, and antihypertensive treatment.1,2,11–13 Finally, we examined the relationship between TLP and several measures of alcohol consumption in age-adjusted and multivariable models. We used the SPSS for Windows 11.0 (SPSS, Chicago, IL).

Correlates of Triple Line Intima-Media Pattern

The TLP was strongly associated with both IMT and plaques. After controlling for age, systolic BP, BMI, TC, HDL cholesterol, glucose, antihypertensive treatment, smoking, and alcohol drinking, the odds of TLP were more than doubled in the presence of carotid plaques (odds ratio=2.42, 95% CI 1.37 to 4.28) and more than 9-fold for each 1 SD of

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The results of multivariate logistic regression (Table 2) show that factors significantly associated with TLP were age, systolic BP, TC, smoking, any alcohol consumption in the last year, and (of borderline significance) IHD. Additional adjustment for presence of plaque attenuated the relationship between TLP and common risk factors but did not fully account for the association between TLP and age, BP, smoking, and alcohol intake (Supplemental Table II). Further adjustment for IMT largely explained the association between TLP and plaques or between TLP and cardiovascular disease risk factors, but not with alcohol.

**Alcohol and TLP**

We examined the association between TLP and alcohol intake (Table 3). For both drinking frequency and annual intake, there was an inverse U-shaped association, with occasional drinkers or those consuming moderate annual amounts of alcohol (second quartile) having the highest risk. The adjusted risk of TLP was more than doubled among binge drinkers who drank 

\[100 \text{ g}
\]

up to 3 times a month; interestingly, the risk of TLP did not seem to be increased in frequent heavy drinkers. The intake of a maximal dose of alcohol on any occasion was associated with an increased likelihood of TLP (odds ratio = 3.18, 95% CI 1.09 to 9.27), but frequent consumption (at least once a week)
of these amounts of alcohol was not significantly associated with an increased risk of TLP.

In further analyses, not shown in tables, we found that IMT was not significantly associated with any of the evaluated measures of alcohol consumption in age-adjusted or multivariable models. However, we found an approximately L-shaped relationship of borderline significance ($P = 0.047$) between the presence of carotid plaque and several measures of alcohol consumption (annual number of drinking sessions, maximal dose of alcohol per session), with the highest risk of plaques among the lowest consumption category.

**Discussion**

In this population sample of middle-aged men in a typical Russian city, we found a high prevalence of subclinical arterial disease, including the striking observation that about one fifth of the men had TLP of the carotid wall. This sonographic pattern was associated with cardiovascular risk factors (most notably BP), IHD, markers of atherosclerosis (IMT, plaques), and with occasional binge drinking but, intriguingly, not with frequent heavy drinking.

**TLP of the Carotid Wall**

The TLP, or similar phenomena, have been reported previously, but earlier reports seemed to suggest that TLP is uncommon and possibly restricted to rare conditions, such as clinically apparent fibromuscular renal dysplasia but in distant arterial sites (carotid, radial). Takayasu arteritis with high inflammatory activity, and pheochromocytoma. However, apart from diabetes and, possibly, asymptomatic fibromuscular dysplasia, which is more prevalent than diagnosed clinically, these conditions are rare in the general population and were not present in our sample. Nevertheless, our study suggests a high prevalence of TLP in men selected from a population with a high rate of cardiovascular disease.

TLP has not been precisely defined previously. To standardize a sonographic definition, we consider TLP as an additional interface within the intima-media compartment of the CCA, which is continuous and expanded through the transducer’s window, and visible in imaging plane in plaque-free area of the arterial wall. We excluded cases with indefinite intima-media inhomogeneity and abnormal layering within atheromatous plaque. We have also shown that identification of the TLP has high interobserver reproducibility in a double-blind assessment.

We were specifically concerned that TLP might be an artifact due to reverberation. To address this issue, we interrogated the abnormal arterial segments in several ways. The insonating frequency on the probe and the beam orientation.

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**Table 3. Odds Ratios (95% CI) for TLP of Carotid Wall by Alcohol Consumption Measure**

<table>
<thead>
<tr>
<th>Alcohol Measure</th>
<th>n</th>
<th>Age-Adjusted Odds Ratio (95% CI)</th>
<th>Multivariable-Adjusted* Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol intake, yes/no</td>
<td>2.21 (0.84 to 5.81)</td>
<td>2.64 (0.95 to 7.35)</td>
<td></td>
</tr>
<tr>
<td>Frequency of drinking, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>49</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;1/mo</td>
<td>70</td>
<td>2.12 (0.71 to 6.33)</td>
<td>2.67 (0.84 to 8.49)</td>
</tr>
<tr>
<td>1–3/mo</td>
<td>94</td>
<td>2.71 (0.95 to 7.75)</td>
<td>3.19 (1.06 to 9.58)</td>
</tr>
<tr>
<td>1–4/wk</td>
<td>183</td>
<td>2.08 (0.76 to 5.68)</td>
<td>2.37 (0.82 to 6.88)</td>
</tr>
<tr>
<td>5+/wk</td>
<td>20</td>
<td>1.50 (0.32 to 7.07)</td>
<td>1.79 (0.35 to 9.24)</td>
</tr>
<tr>
<td>Annual alcohol intake, g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile</td>
<td>105</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Second quartile</td>
<td>103</td>
<td>2.31 (1.14 to 4.66)</td>
<td>2.29 (1.09 to 4.80)</td>
</tr>
<tr>
<td>Third quartile</td>
<td>104</td>
<td>1.73 (0.83 to 3.60)</td>
<td>1.80 (0.83 to 3.91)</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>104</td>
<td>1.41 (0.66 to 3.02)</td>
<td>1.25 (0.56 to 2.81)</td>
</tr>
<tr>
<td>Frequency of binge drinking ($\geq 100$ g per session), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>192</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;1/mo</td>
<td>91</td>
<td>1.97 (1.07 to 3.60)</td>
<td>1.94 (1.02 to 3.70)</td>
</tr>
<tr>
<td>1–3/mo</td>
<td>70</td>
<td>2.20 (1.11 to 4.37)</td>
<td>2.14 (1.03 to 4.43)</td>
</tr>
<tr>
<td>1–5/wk</td>
<td>63</td>
<td>1.10 (0.50 to 2.42)</td>
<td>0.92 (0.40 to 2.12)</td>
</tr>
<tr>
<td>Maximal dose per session %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinkers</td>
<td>49</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;60 g</td>
<td>58</td>
<td>2.24 (0.73 to 6.90)</td>
<td>2.84 (0.86 to 9.33)</td>
</tr>
<tr>
<td>60–99 g</td>
<td>85</td>
<td>1.34 (0.44 to 4.04)</td>
<td>1.70 (0.52 to 5.51)</td>
</tr>
<tr>
<td>100–139 g</td>
<td>81</td>
<td>2.16 (0.74 to 6.34)</td>
<td>2.42 (0.77 to 7.57)</td>
</tr>
<tr>
<td>$\geq 140$ g</td>
<td>143</td>
<td>2.86 (1.06 to 7.87)</td>
<td>3.18 (1.09 to 9.27)</td>
</tr>
</tbody>
</table>

*Adjusted for age, systolic BP, BMI, TC, HDL cholesterol, blood glucose, smoking, and antihypertensive treatment.
tation/angulation were altered, and TLP was verified by visualizing the CCAs both from anterior and lateral planes on the neck, with the appearance of TLP remaining consistent. In a number of randomly selected cases, TLP was observed both in femoral and in carotid arteries, suggesting an influence of systemic factors in the arterial system. Using a high-quality scanner with a matrix probe and increased axial resolution, we demonstrated the location of the additional interface at varying depths from the lumen-intimal interface (supplemental material). These findings do not support the view that TLP is a localized artifact; they rather suggest that the phenomenon is likely to be a genuine reflection of an anatomic substrate.

**Relationship of TLP With Diseases and Risk Factors**

The sonographic TLP of the CCA wall in our study was closely related to IMT thickening, an established phenotypic manifestation of generalized atherosclerosis and arteriosclerosis, and also to carotid plaques as a marker of atherosclerosis burden. This is in line with reports of a similar pattern of gray-level inhomogeneity of CCA intima-media in patients with IHD and in older subjects or alteration of carotid intima-media with an additional layer in diabetic patients. Moreover, TLP was associated with most cardiovascular risk factors (age, systolic BP, TC, smoking) and less strongly with systemic factors in the arterial system. Using a high-quality scanner with a matrix probe and increased axial resolution, we demonstrated the location of the additional interface at varying depths from the lumen-intimal interface (supplemental material). These findings do not support the view that TLP is a localized artifact; they rather suggest that the phenomenon is likely to be a genuine reflection of an anatomic substrate.

Limitations

As this is the first study that found a high prevalence of TLP in a general population sample, morphological data would be extremely valuable, and postmortem histopathologic confirmation will be required.

Our sample did not include women, and this restricts the wider generalizability of our findings. Our study was relatively small, with modest statistical power. However, although lack of power may influence some of the associations between TLP and covariates, it would not be expected to materially affect our estimate of the high prevalence of TLP and its strong relationship to IMT and presence of plaques.

We cannot exclude residual confounding that could affect the relationships between TLP and risk factors. Including women in future studies would be extremely valuable, and postmortem histopathologic confirmation will be required. Our sample did not include women, and this restricts the wider generalizability of our findings. Our study was relatively small, with modest statistical power. However, although lack of power may influence some of the associations between TLP and covariates, it would not be expected to materially affect our estimate of the high prevalence of TLP and its strong relationship to IMT and presence of plaques. We cannot exclude residual confounding that could affect the relationships between TLP and risk factors. Regarding...
alcohol, the only association was found between TLP and episodic, but not regular, drinking; this relationship needs to be interpreted cautiously. For example, TLP risk in frequent heavy drinkers might be underestimated because of their underrepresentation among responders. Nonetheless, there was sufficient variation in exposure in our sample, and alcohol consumption measures have been systematically validated.15,16 We observed consistent results after excluding former drinkers, which reduces the likelihood of misclassification bias due to stopping drinking. Moreover, in the same sample, there was no association of IMT with alcohol, and there was a suggestion of an inverse relationship of plaques with regular drinking; these findings are consistent with the literature, thus supporting the validity of our results.

In conclusion, we have identified a high prevalence of TLP of the carotid wall in a general population sample of men in Russia. This sonographic pattern was strongly associated with established markers of atherosclerosis, such as carotid IMT and plaques, and correlated with most cardiovascular risk factors and diseases, as well as episodic binge drinking. Additional studies are required to confirm these results, elucidate the underlying morphology, and, ultimately, to examine the prognostic value of TLP in prospective investigations.

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Disclosures
None.

References


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Supplemental material

Prevalence and predictors of carotid wall triple line pattern in a general population sample

Ryabikov et al.: Carotid wall triple line pattern

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Table I. Multivariable adjusted associations of common carotid IMT and presence of plaques with TLP of carotid wall (men, 45-69 years old)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid plaques (yes vs no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age-adjusted</td>
<td>2.65 (1.55 – 4.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>multivariable adjusted †</td>
<td>2.42 (1.38 – 4.28)</td>
<td>0.002</td>
</tr>
<tr>
<td>Carotid IMT (per 1SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age-adjusted</td>
<td>8.18 (5.17 – 12.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>multivariable adjusted †</td>
<td>9.53 (5.69 – 15.98)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* CI denotes Confidence Interval.
† Adjusted for age, systolic BP, BMI, total cholesterol, HDL cholesterol, blood glucose, smoking, antihypertensive treatment.
Table II. Relationship between TLP of carotid wall and risk factors adjusted for common carotid IMT and presence of plaques (men, 45-69 years old)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Model 1* Odds ratio (95% CI)</th>
<th>Model 2† Odds ratio (95% CI)</th>
<th>Model 3 ‡ Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.06 (1.02 – 1.10)</td>
<td>0.98 (0.93 – 1.03)</td>
<td>1.05 (1.01 – 1.10)</td>
</tr>
<tr>
<td>Smoking, current/non-smokers</td>
<td>2.11 (1.20 – 3.71)</td>
<td>1.78 (0.86 – 3.67)</td>
<td>1.87 (1.05 – 3.33)</td>
</tr>
<tr>
<td>Systolic BP, per mm Hg</td>
<td>1.01 (1.00 – 1.03)</td>
<td>1.00 (0.99 – 1.02)</td>
<td>1.01 (1.00 – 1.02)</td>
</tr>
<tr>
<td>Total cholesterol, per mmol/l</td>
<td>1.28 (1.01 – 1.61)</td>
<td>1.20 (0.88 – 1.62)</td>
<td>1.24 (0.98 – 1.56)</td>
</tr>
<tr>
<td>HDL cholesterol, per mmol/l</td>
<td>0.65 (0.30 – 1.38)</td>
<td>0.65 (0.22 – 1.86)</td>
<td>0.73 (0.34 – 1.58)</td>
</tr>
<tr>
<td>Alcohol drinking (yes/no)</td>
<td>2.94 (1.05 – 8.27)</td>
<td>3.63 (1.01 – 12.98)</td>
<td>3.22 (1.15 – 9.02)</td>
</tr>
<tr>
<td>BMI, per kg/m²</td>
<td>0.96 (0.89 – 1.03)</td>
<td>0.90 (0.81 – 0.99)</td>
<td>0.97 (0.90 – 1.05)</td>
</tr>
<tr>
<td>Blood glucose, per mmol/l</td>
<td>1.09 (0.94 – 1.27)</td>
<td>1.04 (0.84 – 1.29)</td>
<td>1.07 (0.92 – 1.24)</td>
</tr>
<tr>
<td>Antihypertensive treatment (yes/no)</td>
<td>1.25 (0.66 – 2.34)</td>
<td>1.35 (0.57 – 3.21)</td>
<td>1.14 (0.60 – 2.17)</td>
</tr>
<tr>
<td>Ischemic heart disease (yes/no)</td>
<td>2.18 (0.94 – 5.06)</td>
<td>2.28 (0.77 – 6.70)</td>
<td>1.98 (0.84 – 4.65)</td>
</tr>
</tbody>
</table>

* Adjusted for age, systolic BP, BMI, total cholesterol, HDL cholesterol, blood glucose, smoking, antihypertensive treatment, ischemic heart disease

† as in Model 1 and additionally adjusted for IMT

‡ as in Model 1 and additionally adjusted for presence of carotid plaques
Figure I. Triple line pattern in the femoral artery
Figure II. Varying depth of additional interface in the CCA
**Figure III.** Transverse section of triple line pattern in the CCA
Figure IV. Depth of additional interface within intima-media
Figure V. Triple line pattern in the CCA