IS INTIMAL-MEDIAL THICKNESS A PROPER SURROGATE MARKER FOR SMOKING-ASSOCIATED ATHEROSCLEROSIS?

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Although cigarette smoking is an established risk factor for atherosclerosis, the exact mechanism causing smoking-related damage to the arterial wall and its relation to the atherosclerotic process is not fully understood. Also unknown is the natural course between the start of smoking and the sequence of functional and morphologic changes occurring in the arterial wall caused by smoking.

Carotid intimal-medial thickness (IMT) is often used as a surrogate marker of atherosclerosis. Smoking has been found to be associated with carotid IMT and IMT progression [1,2]. However, others have found no association between IMT or IMT increase with tobacco smoking [2,3]. It is also noted that some harmful effects of smoking on the vessel wall are gender related and smoking may impose more harmful effects upon women than men [4,5].

A recently published study examined the association of smoking status with different echogenic components of carotid arterial wall, i.e. echogenic and echolucent layers in middle-aged adults [6]. Middle-aged men and women who had IMT measurement ≥ 0.7 mm at baseline and 3-yr follow-up in Los Angeles Atherosclerosis Study (LAAS) were included (N = 413, age 40-60 years at baseline in 1995). Intima-media thickness of common carotid artery (CCA-IMT) and its components (echogenic and echolucent layers) were measured at baseline and follow-up examination. IMT and its components were compared across current, former, and never smokers. Individual growth models were used to examine how smoking status was related to the baseline and progression of overall IMT and IMT components. For both men and women, current smoking was associated with thicker echogenic layer than never smokers; former smokers exhibited thinner echogenic layer than current smokers after adjustment for cigarette pack-years. Among women, current smoking was also associated with a thinned echolucent layer that resulted in a non-significant overall association of current smoking with IMT for women. This study suggests that cigarette smoking is associated with carotid artery morphological changes and the association is sex-dependent. The atherogenic effect of smoking appears to be partly reversible among former smokers. IMT measurement alone may not be adequate to detect carotid atherosclerosis associated with cigarette smoking among middle-age women.

B-mode ultrasound imaging can be used to quantify both intimal-medial thickness (IMT) and lumen diameter of extracranial carotid arteries in ambulatory populations. In addition to the findings reported in the above study [6], the association between carotid lumen diameter and cigarette pack-years was assessed among current smokers and never smokers (Figure 1 and 2). In women, the carotid diameter enlarged with accumulative pack-years; the linear trend was significant (p = 0.02 for systolic diameter) or marginally significant (p = 0.07 for diastolic diameter). In men, however, there appears to be a curvilinear association between lumen diameter and cigarette dose (p for cubic trend = 0.09). A decrease-increase-decrease pattern for carotid lumen diameter was manifested.
with increased cigarette pack-years. Noticeably, the trend for the echolucent layer thickness was in the opposite direction as the lumen diameter. The echolucent layer thickness significantly declined with increased cigarette dose (p for linear trend = 0.005) in women, whereas there was a curvilinear trend in men (p = 0.009 for quadratic trend), i.e. an increase-decrease pattern for echolucent layer thickness was manifested with cigarette dose. The association of lumen diameter at systole with cigarette pack-years was similar to that for diastole. For simplicity, only lumen diameter change for diastole was shown.

Arterial remodeling in response to atherosclerosis may occur in the form of compensatory enlargement and/or focal vessel contraction [7,8]. There was evidence that smoking is related to arterial compensatory enlargement [9], or to focal contraction [7]. In the current study, the association of lumen diameter change with the smoking dose was curvilinear for men. Considering the pattern of echolucent layer (approximately corresponding to the central media layer) change, the curvilinear pattern could be explained as follows. In lower cumulative pack-years, vasoconstriction occurs as a response to the toxic effects of smoking; as cigarette pack-years accumulate, attenuated vasoregulation coupled with thinned media causes compensatory vessel enlargement; with further pack-year accumulation, vessel constriction reoccurs in response to damaged arterial wall and increased stiffness.

The LAAS study provides evidence that the echolucent layer (most likely corresponding to medial layer) which is a major component of IMT may not necessarily thicken during the smoking-related atherosclerotic process. The thinned echolucent layer may be caused by smoking-induced smooth muscle cell apoptosis [7] and consequent medial atrophy and media stretching without a compensatory increase in matrix protein synthesis. Smoking is an important risk factor for the development of abdominal aortic aneurysms (AAA) [10]. The histopathology of aortic aneurysms is dominated by a transmural degenerative process characterized by medial atrophy, a gradual thinning and weakening of the vessel wall, and dilation or expansion of the aorta [9]. Therefore, if the smoking-related atherosclerosis in the common carotid is similar to that in the abdominal aorta (both are elastic-type arteries), the thinning carotid echolucent layer found in our study may be attributed to the medial atrophy.

The efforts to distinguish the smoking effects on different echogenic components of IMT afford unique opportunity to study pathogenesis of atherosclerosis. Another study compared echogenic features of ultrasound-detected carotid plaques caused by LDL cholesterol and smoking [11]. It is found that LDL cholesterol was relatively more associated with echolucent plaques, while smoking was associated with echogenic plaques. Thus it suggests that LDL cholesterol may be of key importance both in plaque initiation and vulnerability to rupture, whereas smoking may relate to plaque progression to thicker, more fibrous lesions.

The LAAS study offers evidence that tobacco smoking may impose AAA-like effects. The thinning medial layer thickness and dilation of lumen diameter are closely associated. This may explain why cigarette smoking is not associated with brachial blood pressure in most studies and may even be associated with greater distensibility which was calculated from the change in carotid diameter over the cardiac cycle [11]. This may also explain why some studies failed to find a direct association of tobacco smoking and IMT as among women in the LAAS study. Thus IMT itself may not be an ideal indicator for...
early atherosclerosis caused by smoking; using arterial distensibility as a functional marker for arterial stiffness may reach spurious conclusion [11]. In fact, tobacco exposure is associated with impaired endothelial function and arterial stiffness as indicated by increased augmentation index (AIx) [12], lower ankle-brachial index (ABI) [13], and dose-related impairment of endothelium-dependent (flow-mediated) dilation (FMD) of peripheral artery [4] which may precedes morphologic changes of the vessel wall.

In view of the complex nature of atherosclerosis caused by cigarette smoking and limitation of IMT, researchers in the field are cautioned to use IMT as a surrogate indicator of subclinical atherosclerosis. Other available measures should be considered including imaging techniques such as plaque areas by b-mode ultrasound [14], and functional indicators such as AIx, ABI, or FMD.

References

6. Fan AZ, Paul-Labrador M, Merz CNB, Iribarren C, Dwyer JH. Smoking status and common carotid artery intima-medial thickness among middle-aged men and women based on ultrasound measurement: a cohort study. The electronic version of this article can be found online at: http://www.biomedcentral.com/1471-2261/6/42 BMC Cardiovascular Disorders 2006;6(42):42.
Figure 1. Carotid lumen diameter for diastole (left axis) and echolucent-layer thickness (right axis) by smoking pack-year categories for women. Data are least-square mean ± SE, controlled for age, height, and ethnicity. Category 0 was for never smokers, and categories 1-3 were determined by the tertiles of smoking pack-year.
Figure 2. Carotid lumen diameter for diastole (left axis) and echolucent-layer thickness (right axis) by smoking pack-year categories for men. Data are least-square mean ± SE, controlled for age, height, and ethnicity. Category 0 was for never smokers, and categories 1-3 were determined by the tertiles of smoking pack-year.