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Risk Factors for Atherosclerosis and the Development of Pre-Atherosclerotic Intimal Hyperplasia

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Abstract

Summary—Intimal hyperplasia or thickening is considered to be the precursor lesion for atherosclerosis in humans; however the factors governing its formation are unclear. In the atherosclerosis-resistant internal thoracic artery, pre-atherosclerotic intimal hyperplasia routinely forms during adulthood after the 4th decade and is associated with at least two traditional risk factors for atherosclerosis: age and smoking.

Background—Intimal hyperplasia, or thickening, is considered to be the precursor lesion for atherosclerosis in humans; however, the factors governing its formation are unclear. To gain insight into the etiology of pre-atherosclerotic intimal hyperplasia, traditional risk factors for atherosclerosis were correlated with the intimal hyperplasia in an atherosclerosis-resistant vessel, the internal thoracic artery.

Methods—Paired internal thoracic arteries were obtained from 89 autopsies. Multivariate logistic regression and multiple regression models were used to examine the association of pre-atherosclerotic intimal hyperplasia with traditional risk factors for atherosclerosis: age, gender, hypertension, smoking, body mass index, diabetes, and hypercholesterolemia.

Results—Atherosclerotic lesions consisting of fatty streaks and/or type III intermediate lesions were identified in 19 autopsies. Only age >75 years was found to be significantly correlated with atherosclerotic lesion development ($P=0.01$). Multiple regression model of the intima/media ratio in all 89 cases revealed age >75 years ($P<0.0001$), age 51–75 years ($P=0.0012$), smoking ($P=0.008$) and hypertension ($P=0.02$) to be significantly correlated with intimal thickness. In the 70 cases without atherosclerosis, only age 51–75 years ($P=0.006$) and smoking ($P=0.028$) were found to be significantly associated with pre-atherosclerotic intimal thickening.

Conclusions—In the atherosclerosis-resistant internal thoracic artery, pre-atherosclerotic intimal hyperplasia routinely forms during adulthood after the 4th decade and is associated with at least two traditional risk factors for atherosclerosis: age and smoking. These observations indicate that in some settings, intimal hyperplasia may be part of the disease process of atherosclerosis, and that its formation may be influenced by traditional risk factors for atherosclerosis.

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Keywords

intimal hyperplasia; intimal thickening; intima; atherosclerosis; smoking; hypertension; body mass index; age; diabetes

1. Introduction

In humans and in pigs fed a high-fat diet, atherosclerotic lesions have been shown to develop at sites of preexisting intimal thickening or intimal hyperplasia [1–4]. These early hyperplastic lesions are composed predominantly of smooth muscle cells in a proteoglycan rich matrix with small numbers of macrophages and without evidence of substantial foam cell formation or extracellular lipid deposits. The precise etiology of this intimal hyperplasia is unclear, although it may be related to that of the intimal cushions or pads that form at branch sites in the vasculature [5,6]. Pre-atherosclerotic intimal hyperplasia forms invariantly in humans in the highly atherosclerosis susceptible post-branch region of the proximal left anterior descending coronary artery within the first decade of life [5,7]. The early and universal presence of this lesion in the coronary arteries has made studies into its etiology difficult.

However, not all human arteries develop this pre-atherosclerotic intimal hyperplasia at post-branch locations to the extent seen in the coronary arteries. In particular, the atherosclerosis-resistant internal thoracic arteries have been documented to show essentially no intimal hyperplasia during the first 5 decades of life [8]. However intimal hyperplasia and even atherosclerotic lesions, have been reported to occur in the internal thoracic arteries of older individuals [9–13]. The development of pre-atherosclerotic intimal hyperplasia in atherosclerosis-resistant arteries in older individuals offers the opportunity to assess for the association of classic risk factors for atherosclerosis with the development of intimal hyperplasia. Previous studies along this line have yielded inconsistent results as to a relationship between intimal hyperplasia in the internal thoracic artery and traditional risk factors for atherosclerosis [9–12]. However, these studies have been limited by several factors including apparent relatively random sampling of the vessel, and the inclusion of other lesion types in the analysis, particularly fatty streaks and advanced atherosclerotic lesions. The presence of atherosclerotic lesions confounds to even a greater degree attempts to associate atherosclerosis risk factors with intimal hyperplasia in other arteries such as the radial artery, which although relatively resistant to atherosclerosis, is still more susceptible to atherosclerosis than the internal thoracic artery [9,11,14,15].

To assess the relationship of traditional risk factors for atherosclerosis with specifically intimal hyperplasia, the internal thoracic arteries were examined from 89 autopsies, after exclusion of all cases in which injury to the vessel may have been sustained by an alternative mechanism, such as surgery, radiation therapy or systemic vasculitis. Importantly a post-branch site was selected for analysis, 0.5 cm distal to the branching of the 2nd intercostal artery in the 2nd intercostal space. This analysis reveals that in the atherosclerosis-resistant internal thoracic artery, intimal hyperplasia occurs after the fourth decade of life and occurs largely prior to fatty streak and atherosclerotic lesion formation. In addition by multiple regression analysis, both age and smoking were found to independently associate with the formation of intimal hyperplasia in this vessel.

2. Methods

2.1. Arterial Segments

Internal thoracic arteries and clinical history were evaluated for 130 autopsies performed at Massachusetts General Hospital during 2004–2006, on patients ranging in age from the 2nd

to the 10th decades of life. Inclusion criteria for these 130 cases were an autopsy permission by the next of kin allowing tissue to be utilized for research and the absence of exclusion criteria. The exclusion criteria for obtaining these 130 cases were a post-mortem interval greater than 48 hours or the presence of hepatitis B or HIV infection. Patient medications were not utilized for either inclusion or exclusion criteria. The study was approved by the hospital's Human Subjects Institutional Review Board. Of these 130 cases, 23 cases were excluded due to a lack of available clinical information, and 14 cases were excluded due to a history of thoracic surgery and/or thoracic radiation therapy (Fig. 1A). An additional two cases were excluded due to the presence of systemic vasculitis involving the internal thoracic arteries (Fig. 1B). As statistical outliers, one case of morbid obesity [body mass index (BMI) =79 kg/m²] was excluded, as was one case with advanced atherosclerosis of the internal thoracic arteries in an 87 year old woman (Fig. 1C). The right and left internal thoracic arteries were sampled for histologic analysis at 0.5 cm distal to the branching of the 2nd intercostal arteries in the 2nd intercostal spaces. Arterial rings 2mm in thickness were fixed in formalin, paraffin embedded, and stained with hematoxylin and eosin as described previously [16].

2.2 Histologic Assessment

Intima and medial thickness measurements were obtained on hematoxylin and eosin stained slides as described previously [16] and used to generate the intima/media ratio. For each patient, the two intima/media ratio values were averaged for statistical analysis. Atherosclerotic lesion types were determined using previously reported definitions [3,17]. Intimal hyperplasia is here defined as a thickened intima without foam cells or extracellular lipid deposits. For the purposes of this study, lesions containing foam cells indicating a fatty streak or intimal xanthoma were defined as atherosclerotic lesions, as were more advanced type III intermediate lesions [17], which have also been referred to as pathologic intimal thickening [4]. Each patient was assigned a lesion type of either atherosclerotic or non-atherosclerotic based on the most severe lesion identified from either side. For each of the 89 patients in the study, the cause of death was categorized as either coronary artery disease, stroke, malignancy, infection, neurodegenerative disease or other. The other category consisted of primary cardiomyopathies, valvular heart diseases, amyloidosis, pulmonary fibrosis, cirrhosis, asthma, and myocarditis.

2.3 Risk Factors

For each patient, the clinical history was evaluated for age, gender, smoking history, non-insulin dependent diabetes mellitus (NIDDM), hypertension, BMI, and hypercholesterolemia. A non-smoker was defined as someone who never smoked. Hypertension and NIDDM were defined as a patient with that clinical diagnosis whether treated or not. Here, hypercholesterolemia was defined as either (1) having a clinical diagnosis of hypercholesterolemia and being treated for hypercholesterolemia, or (2) having a fasting total serum cholesterol level >240 mg/dL. Of the 17 patients defined as having hypercholesterolemia, all but 3 were being treated for the condition, primarily with statin derivatives. Total serum cholesterol levels were available for 15 of these 17 patients, and measured 240±54 mg/dL (mean±standard deviation). For patients defined as having hypercholesterolemia who did not have atherosclerosis in the internal thoracic arteries, total serum cholesterol levels were available for 10 of 12 patients, and measured 251±49 mg/dL. BMI was calculated from height and weight at the time of death and was expressed in units of kg/m². BMI data was not available for 3 of the 89 patients. Information on hypercholesterolemia was not available for 3 of the 89 patients.

2.4 Statistical Analyses

Patients were placed into 1 of 3 age groups, 20–50 years, 51–75 years or greater than 75 years. Univariate analysis comparing intima/media ratio versus age group was performed using the

student's t test. Univariate analysis comparing atherosclerotic lesion development with age group was performed using Fisher's exact test. For all 89 cases, including those with atherosclerotic lesions, multivariate logistic regression model was used to determine the odds ratio for atherosclerotic lesion development associated with each of the atherosclerotic risk factors. Multiple regression analysis was performed on all 89 cases with the log of the intima/media ratio as the dependent variable because the outcome was skewed. We also performed a multiple regression analysis including only the 70 cases not containing atherosclerosis with intima/media ratio as the dependent variable. For this study, p values less than 0.05 were considered significant.

3. Results

3.1. Cases Excluded

For this study, it was important to exclude cases in which other causes may have contributed to the formation of intimal hyperplasia, such as thoracic radiation therapy (Fig. 1A). In addition upon review of the histology, two cases were found to contain active vasculitis, one of which was in a patient with florid systemic Lupus vasculitis (Fig. 1B). Vasculitis involving the internal thoracic arteries has been reported previously [18]. In both of the cases of vasculitis excluded here, the histology demonstrated an inflammatory infiltrate consisting of macrophages and lymphocytes associated with damage to the media in the absence of advanced atherosclerosis.

3.2. Histologic Analysis

The vessels not otherwise excluded showed pathology ranging from normal (Fig. 2A) with no intimal thickening to one case with an advanced type V fibroatheroma (Fig. 1C). This latter case was excluded from the statistical analysis, as an outlier due to an unusually large intima/media ratio. Of the 89 cases included in the study, there were 70 cases that demonstrated either normal histology or intimal hyperplasia, 17 cases showing fatty streaks, and 2 cases with type III intermediate lesions (Fig. 2). The lesions in these post-bifurcation arterial segments were predominantly eccentric.

3.3. Association of Atherosclerosis Risk Factors

The characteristics of the 89 patients in this study are listed in Table 1. A plot of the intima/media ratio versus age (Fig. 3) demonstrates an expansion of the intima after the 4th decade of life by intimal hyperplasia. This predominantly hyperplastic phase is then followed by atherosclerotic lesion formation occurring primarily after the 7th decade. By multivariate modeling relating atherosclerotic lesion formation with risk factors, age > 75 years was the only risk factor found to have a significant association (Fig. 4).

For all 89 cases, which includes those with atherosclerosis, multiple regression model relating the log of the intima/media ratio with risk factors revealed significant independent associations with age > 75 ($p < 0.0001$), age 51–75 ($p = 0.001$), smoking ($p = 0.008$) and hypertension ($p = 0.023$). Hypercholesterolemia was close to the cutoff for significance ($p = 0.052$). There was no significant association with NIDDM, gender, or BMI. For the 70 cases without atherosclerosis, multiple regression model relating the intima/media ratio with risk factors revealed significant independent associations with age 51–75 years ($p = 0.006$) and smoking ($p = 0.028$). Age > 75 years was just outside the range of significance ($p = 0.055$), due most likely to the low number of patients free from atherosclerosis in this age group. There was no significant independent association of the pre-atherosclerotic intima/media ratio with hypertension, NIDDM, hypercholesterolemia, gender or BMI.

4. Discussion

Pre-atherosclerotic intimal hyperplasia develops universally within the first decade in the atherosclerosis-prone coronary arteries, making studies into its etiology difficult. The slower course of development of intimal hyperplasia in atherosclerosis-resistant arteries offers the opportunity to study the relationship between potential causative factors and intimal hyperplasia at these sites. Although the site for such a study should be chosen with caution, as medium-sized arteries in trauma-susceptible locations, such as the distal ulnar artery, readily develop intimal hyperplasia that is probably not related to the atherosclerotic process [16]. In this regard, the internal thoracic artery is an ideal choice for study due to its documented resistance to atherosclerosis and its relatively protected location.

A few previous studies have sought to assess the relationship of early and pre-atherosclerotic changes in the internal thoracic artery with classic risk factors for atherosclerosis (Table 2). An initial study on 215 autopsies revealed, by univariate analysis, significant association of intimal thickness with age and hypertension but not diabetes [10]. Smoking was not assessed. In a subsequent study evaluating the internal thoracic arteries from 160 autopsies, by univariate analysis there was a significant association of intimal thickness with hypertension, but not age, smoking, diabetes, or BMI [12]. More recently two studies have addressed the same question using portions of distal internal thoracic artery obtained at the time of coronary artery bypass grafting. In the first of these studies, evaluation of 64 internal thoracic arteries by multivariate model revealed no significant association of intimal thickness with age, hypertension, smoking, diabetes, hypercholesterolemia, or gender [9]. In a subsequent study, multivariate modeling with 110 resected internal thoracic arteries revealed only age to have a significant association with intimal thickness, with no significant association with hypertension, smoking, diabetes, hypercholesterolemia or gender [11]. However, in that study, intimal area was significantly associated with both age and smoking.

These studies raised the possibility that risk factors for atherosclerosis such as age, smoking, and hypertension may influence the development of pre-atherosclerotic intimal hyperplasia in relatively atherosclerosis-resistant vessels. However, a significant concern with these studies was that other lesion types such as fatty streaks and even type III intermediate lesions were included in the analyses, making it unclear if the potential effects of the risk factors were on the formation of intimal hyperplasia or simply the progression of intimal hyperplasia to atherosclerotic lesions. By focusing on a defined post-branch location and by excluding cases where other processes may be contributing to the intimal thickening, the analysis here indicates that age, smoking, and hypertension are all independently associated with intimal thickness when assessing both pre-atherosclerotic intimal hyperplasia in conjunction with fatty streaks and type III intermediate lesions. However, when the fatty streaks and type III intermediate lesions are excluded, only age and smoking are significantly associated with intimal thickness. This analysis draws attention to smoking as the major modifiable risk factor associated with pre-atherosclerotic intimal hyperplasia in the internal thoracic artery of adults.

The association of age with intimal hyperplasia was expected considering the general association of age with intimal thickening throughout the body [6], and the identification of the association in two of the four previous studies listed in Table 2. This association with age likely represents a manifestation of the ageing of human arteries, which is poorly understood. Even though hypertension was also found to be associated with intimal thickness in the two previous univariate studies in Table 2, the close linkage of hypertension with age (Table 1), explains why hypertension was not observed to independently associate with intimal hyperplasia in this study. As the two previous multivariate studies listed in Table 2 also failed to identify an association of intimal thickness with hypertension, this result was not unexpected. The association of smoking with pre-atherosclerotic intimal hyperplasia observed here was

somewhat unexpected. Smoking is clearly associated with atherosclerotic lesion formation; however, no previous study had definitively linked smoking with intimal thickness of pre-atherosclerotic lesions in medium-sized arteries. In fact the three previous studies listed in Table 2 that examined smoking, all failed to find an association with intimal thickness, even though these studies included some atherosclerotic lesions. Although one study did report an association with intimal area. The cause of the association of intimal hyperplasia with smoking is not known but may involve a direct activation of the vessel wall by agents introduced into the circulation upon smoking.

The etiology of pre-atherosclerotic intimal hyperplasia has remained elusive. The current and previous studies on the internal thoracic artery indicate that hypercholesterolemia does not appear to play a significant role in this process, consistent with the notion that the effect of elevated cholesterol is primarily to stimulate lipid deposition in an intima that already exhibits intimal hyperplasia [1–4]. Correspondingly, the plot in Fig. 3 would support the view that, in general, intimal hyperplasia precedes fatty streak formation [7,19]. Since intimal hyperplasia is universal in the coronary arteries in the first decade of life, studies on the factors associated with its formation in these vessels have been limited [20]. Interestingly, a recent study has reported that intimal hyperplasia in the coronary arteries of infants age 1 to 36 months is significantly correlated with smoking by the parents [21]. While parental smoking cannot account for all coronary artery intimal hyperplasia, that study is consistent with our observation that environmental factors, particularly smoking, are associated with the formation of pre-atherosclerotic intimal hyperplasia.

This association of smoking with intimal hyperplasia raises an important implication for the role of smoking in atherosclerosis, specifically that smoking may play a role in the earliest phases of lesion development. While intimal hyperplasia is universal in the coronary arteries within the first decade of life, this is not the case in other clinically important although slightly less atherosclerosis-prone arteries. For example, some people do achieve adulthood without the formation of intimal hyperplasia in the proximal internal carotid artery [13]. Smoking, particularly in adolescence, may help set the stage for atherosclerosis at these clinically important sites by first stimulating formation of intimal hyperplasia.

Limitations of this study include the fact that most of the patients with hypercholesterolemia, hypertension, and diabetes were being treated for these conditions, and it can not be ruled out that these treatments may have mitigated any potential influences of these diseases on the formation of intimal hyperplasia. Also the number of patients with diabetes and/or hypercholesterolemia in this study is relatively small, and relatively minor contributions of these disorders to intimal hyperplasia cannot be excluded. As another limitation, the determination of smoking status, either current or former, was derived from clinical history only. Also, the plot in Figure 3 implies a temporal progression from normal to intimal hyperplasia to early atherosclerosis, but it should be kept in mind that these are single measurements in time, and thus the inferred temporal relationship is actually derived indirectly.

An interesting finding in this study was the relatively high rate of fatty streak and/or type III intermediate lesion formation in the internal thoracic artery in the 9th and 10th decades of life. In fact, the internal thoracic arteries in this advanced age group resemble the coronary arteries in individuals in the 2nd and 3rd decades [17,22]. This observation not only reinforces the concept of age as an important risk factor for atherosclerosis, but it also suggests that when considering the relative resistance of an artery to atherosclerosis, the issue may be not so much *if* the artery will develop atherosclerosis, but rather *when* will the artery develop atherosclerosis.

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Fig. 1.

Examples of Cases Excluded from This Study. Shown are hematoxylin and eosin stained sections. A. An artery with transmural fibrous scarring from an 80 year old woman who had received radiation therapy for breast carcinoma (x200). B. Active vasculitis in a 60 year old man with systemic Lupus vasculitis (x200). C. An unusual example of an advanced type V fibroatheroma in an 87 year old woman (x100).

Fig. 2.

Examples of the Intimal Lesions Included in the Study. Shown are hematoxylin and eosin stained sections. A. A normal artery in a 36 year old (x200). B. An artery with intimal hyperplasia from a 53 year old (x200). Arteries showing fatty streak formation (C, x200) and a type III intermediate lesion (D, x100) from patients over the age of 89. The arrows indicate the intima/media boundaries.

Fig. 3.

Intimal Thickness in the Internal Thoracic Artery. Shown is a plot of the intima/media ratio versus age, with each patient being represented by one closed circle. Those with atherosclerotic lesions (fatty streaks or type III intermediate lesions) are in red, all others are black. The non-atherosclerotic intimal thickness (black circles) was significantly greater in those age 51–75 years than in those age 20–50 years. The presence of atherosclerotic lesions (red circles) was significantly greater in those over the age of 75 years, than in those age 51–75 years. To comply with privacy regulations, for all patients over the age of 89, the data is arbitrarily plotted at age 95. P values represent univariate analyses as detailed in the methods section. For non-atherosclerotic intimal thickness, the intima/media ratio depicted by the black circles was compared between the age groups indicated by the brackets. For atherosclerotic lesion formation, the proportion of cases with atherosclerotic lesions (red circles) was compared between the age groups indicated by the brackets. NS=not statistically significant.

Fig. 4. Risk Factors and Atherosclerotic Lesion Formation. Shown are the point estimates and 95% confidence intervals for the odds ratio for each of the listed risk factors. Only age greater than 75 years demonstrated a significant association with atherosclerotic lesion formation.

Table 1

Patient Characteristics

Age Group (years)	All Cases				Normal and Intimal Hyperplasia Only			
	20-50	51-75	>75	Total	20-50	51-75	>75	Total
Number	18	47	24	89	17	43	10	70
Male Gender	14	32	11	57	13	28	6	47
Age (Mean±SD)	39±8	61±7	84±6	63±17	39±8	60±6	82±6	58±15
Hypertension	4	14	20	38	4	12	7	23
Smoking	11	24	11	46	10	20	5	35
NIDDM	3	8	6	17	2	8	4	14
Hypercholesterolemia	2	8	7	17	2	7	3	12
BMI (kg/m ² , Mean±SD)	29±9	26±8	24±7	27±8	29±10	27±8	28±10	28±9
Atherosclerotic Lesions	1	4	14	19	0	0	0	0
Causes of Death								
Coronary Artery Dis.	1	1	6	8	1	1	1	3
Stroke	2	3	5	10	2	3	1	6
Malignancy	5	15	4	24	5	14	3	22
Infection	4	10	6	20	3	9	3	15
Neurodegenerative Dis.	1	9	0	10	1	9	0	10
Other	5	9	3	17	5	7	2	14

Table 2
Studies Relating Intimal Thickness in the Internal Thoracic Artery with Risk Factors for Atherosclerosis

Study	Lesion Types	Statistical Method	Mean Age	Age ^a	HTN	Smoking	Ref.
215 Autopsies	All	Univariate	60	<0.01	<0.01	---	[10]
160 Autopsies	All	Univariate	63	N.S.	0.025	N.S.	[12]
64 Surgicals	All	Multivariate Modeling	62	N.S.	N.S.	N.S.	[9]
110 Surgicals	All	Multivariate Modeling	66	0.012	N.S.	N.S. ^d	[11]
89 Autopsies	All	Multivariate Modeling	63	<0.0001 ^b	0.023	0.008	This work
70 Autopsies	Intimal Hyperplasia	Multivariate Modeling	58	0.006 ^c	N.S.	0.028	This work

^aFor age, hypertension (HTN), and smoking, p values are listed for observed significant association with intimal thickness. N.S. = not significant.

^bFor age > 75.

^cFor age 51–75.

^dA significant association was observed (p < 0.001) with smoking and intimal area, but not with intimal thickness.