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Thrombosis in the Young: Effect of Atherosclerotic Risk Factors on the Risk of Myocardial Infarction Associated with Prothrombotic Factors

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Introduction

Numerous studies have examined the relation of risk factors for atherosclerosis and thrombosis with the occurrence of myocardial infarction, particularly among middle-aged and older adults. However, few studies have examined the joint effects of these risk factors on the risk of myocardial infarction. Given the characteristic athero-thrombotic pathology of myocardial infarction, it is reasonable to speculate that the joint effects of atherosclerotic and thrombotic risk factors on the risk of myocardial infarction may be greater than the effects of these factors considered separately.

In this paper, we review the pathologic, clinical, and epidemiolgic evidence that suggests the interaction of atherosclerotic and prothrombotic factors influences the risk of myocardial infarction, particularly among the young. We summarize the findings from a study of myocardial infarction in young women that suggests that the joint effects of a prothrombotic risk factor, factor V Leiden, and other risk factors, including smoking and obesity, on the risk of myocardial infarction is particularly large (1). In the absence of other risk factors, the prothrombotic risk factor was not associated with the risk of myocardial infarction. Based upon these preliminary observations, we hypothesize that prothrombotic risk factors interact synergistically with atherosclerotic risk factors to increase the risk of myocardial infarction.

Pathophysiology of athero-thrombotic disease

Thrombosis of a coronary artery typically occurs in the setting of coronary atherosclerosis and results in the clinical occurrence of acute myocardial infarction (2). Recent studies suggest that the disruption of a complex, lipid-laden, atherosclerotic plaque precipitates the occurrence of an occlusive coronary thrombosis (2). Additionally, myocardial infarction frequently occurs at sites of previously nonsevere coronary lesions (3), and the severity of coronary stenosis does not accurately predict the location of a subsequent coronary occlusion (4). For these reasons, it is likely that interactions between atherosclerosis and thrombosis influence the risk of myocardial infarction.

Although non-atherosclerotic causes of myocardial infarction occur among the young, myocardial infarction in the young usually occurs in the presence of coronary atherosclerosis and thrombosis (5,6). Among young adults who experience myocardial infarction, the prevalences of both normal coronary artery anatomy (range 8-17 percent) and single-vessel disease (range 32 to 62 percent) are higher and the prevalences of severe (>70% stenosis) and multivessel disease lower than among older adults with myocardial infarction (6). In short, the contribution of thrombosis to athero-thrombotic disease may be particularly important in the young.

Factors related to myocardial infarction

Both older age and male gender are strongly associated with the incidence of myocardial infarction: myocardial infarction is rare among persons less than 45 years of age and the incidence is particularly low among young women (7). Among the young, myocardial infarction occurs rarely in the absence of major coronary heart disease (atherosclerotic) risk factors; and, multiple risk factors, including current smoking, obesity, hypercholesterolemia, hypertension, and diabetes, are typically present (8,9). These factors also are associated with the risk of myocardial infarction among the middle-aged; however, the associations, as reflected by estimates of relative risk, are particularly large among young persons.

The risk factors associated with myocardial infarction in the young differ among those with and without obstructive coronary (atherosclerotic) disease (10). Among cases of myocardial infarction in the young with obstructive coronary artery disease, there were high prevalences of cigarette smoking, hypercholesterolemia and hypertension (10). In contrast, the sole major risk factor identified among cases of myocardial infarction in the young with normal coronary arteriograms was heavy smoking (10).

Studies conducted in the 1960's and 1970's demonstrated that among premenopausal women, a particularly low incidence population, the current use of the high dose (estrogen) oral contraceptives was associated with a particu-

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larly large increase in the risk of myocardial infarction among current smokers (11,12). High dose (estrogen) oral contraceptives have multiple potential adverse (lipid, glucose, and hemostasis) metabolic effects, and cigarette smoking is associated with both atherosclerosis and thrombosis. Of note, the joint effects of the use of high dose oral contraceptives and current smoking was far greater than the separate effects of these factors: an observation that was consistent with a synergistic interaction.

Frequency of risk factors for atherosclerosis

The prevalences of risk factors for atherosclerosis vary by age and gender. The prevalences of risk factors related to atherosclerosis, including obesity, hypercholesterolemia, hypertension, and diabetes, increase markedly during middle-age, possibly because of an age-related increase in viseral adiposity and a decline in physical activity (7). In contrast, the prevalence of current cigarette smoking is highest among young adults and lowest among the elderly, in part, because of the impact of smoking on survival and the higher quit rates among older adults. Among women, menopause is associated with both changes in risk factor levels and an increase in the risk of myocardial infarction (13). For oral contraceptives, the prevalence is highest among younger pre-menopausal women and declines to less than 4 percent among women ages 40-44 in the USA (7).

Familial aggregation of myocardial infarction

The association of the family history of myocardial infarction at an early age in a first-degree relative with the occurrence of myocardial infarction is particularly strong among the young (14). However, the extent to which the observed familial aggregation of myocardial infarction among the young reflects shared genetic factors, shared environmental factors, or the interaction of shared genetic and environmental factors within families remains unknown. Because myocardial infarction is a complex disease, it is unlikely that a single gene or several genes explain the occurrence of myocardial infarction, even among the young. Given the strong association of behavioral risk factors, such as cigarette smoking and physical inactivity, and metabolic risk factors, such as obesity, hypercholesterolemia, hypertension, and diabetes, with the risk of myocardial infarction, it is reasonable to speculate that multiple genetic and environmental factors interact in the etiology of myocardial infarction.

Genetic factors and atherosclerosis

In general, heritable factors related to atherosclerosis may be more important in the young than in the old (15). Hereditary abnormalities of lipid and lipoprotein metabolism, such as familial hypercholesterolemia, are associated with an increased risk of premature atherosclerosis and myocardial infarction. While moderate elevations of LDL-cholesterol are associated with atherosclerosis, the rare genetic disorders that result in severe hypercholesterolemia account for a only small proportion of the cases of myocardial infarction, even among the young. Elevated levels of lipoprotein (a), another factor that is determined, at least in part, by genetic factors, also may increase the risk of atherosclerosis and/or thrombosis and are related to the risk of myocardial infarction in the young women(16). However, among middle-aged populations, findings related to a possible relation between Lp(a) and the risk of myocardial infarction have been inconsistent (17).

Risk factors for thrombosis

Among middle-aged men, markers of hemostatic risk have been associated with the risk of myocardial infarction. In the Northwick Park Heart Study, both the levels of factor VII coagulant activity and plasma fibrinogen were associated with an increased risk of non-fatal myocardial infarction and ischemic heart disease death among middle aged men, especially during the first 5 years of follow-up (18). Of note, the risk of ischemic heart disease associated with high fibrinogen was greater in younger than in older men (18). Plasma D-dimer levels at the upper end of the distribution were associated with an increased risk of myocardial infarction among middle-aged men in the Physicians Health Study (19), suggesting that activation of the endogenous fibrinolytic system may occur long in advance of the coronary occlusion that results in acute myocardial infarction. However, after adjustment for total and HDL cholesterol, the increase in risk associated with a high D-dimer level was no longer statistically significant (19). Elevated endogenous tissue-type plasminogen activator (t-PA:ag) and its primary inhibitor, plasminogen activator inhibitor type one (PAI-1) also were directly associated with the risk of myocardial infarction in the Physicians Health Study, particularly among younger men (20).

Whether markers of the balance of the coagulation and fibrinolytic systems are independently related to the risk of myocardial infarction remains unclear, in part, because the levels of these hemostatic markers are associated with both other risk factors and atherosclerosis (21-32). For example, plasma fibrinogen is associated with other risk factors, such as smoking and physical inactivity, and fibrinogen also is a marker of underlying low-grade inflammation. Obesity, lipids, alcohol consumption, estrogen replacement therapy, gemfibrozil and angiotensin converting enzyme inhibitors are associated with the endogenous fibrinolytic balance (24-30). In general, behavioral changes aimed at reducing blood pressure and improving lipid profiles, including exercise, diet, and moderate alcohol consumption, also may result in favorable alterations in Factor VII activity and PAI-1 (21-23).

Genetic mutations and thrombosis

Several studies have examined the association of genetic mutations related to thrombotic markers, such as the Beta-fibrinogen gene and PAI-I promoter, with myocardial infarction (33-35). Beta-fibrinogen G/G genotype was associated with a two fold increase in the risk of myocardial infarction;

and, the association with coronary artery disease was particularly strong among women (33). In a Swedish study among men <45 years old, the 4G allele in the promoter of the plasminogen activator inhibitor gene was associated with a two-fold increase in the risk of myocardial infarction (35). However, the 4G/5G polymorphism in the promoter of the PAI-1 gene was not associated with myocardial infarction among the participants in the Physicians Health Study (34). Additionally, several studies have examined the relation of a polymorphism of platelet glycoprotein IIIa with the risk of myocardial infarction, but the results have been inconsistent (36-38). The physiologic consequences of the polymorphism of the platelet glycoprotein IIIa remain unclear; for this reason, it is unclear whether there is a plausible pathophysiological mechanism for an association with myocardial infarction (39).

Although deficiencies of protein C (PC), protein S (PS), and antithrombin (AT) are uncommon, these deficiencies are associated with venous thrombosis (40,41). Whether deficiencies of PC, PS and AT are associated with the risk of myocardial infarction among the young remains unclear. The carriership of Factor V (Leiden) mutant gene related to resistance to activated protein C occurs in 4-5 percent of the population; and it is clearly associated with an increased risk of venous thrombosis (42). However, findings of studies that have examined the association between factor V-Leiden and the risk of myocardial infarction are inconsistent (1,43).

Recently, we explored the role of factors related to thrombosis and other factors potentially related to atherosclerosis in the etiology of myocardial infarction among young women, 18-44 years of age. As part of a population-based case-control study of low-dose estrogen oral contraceptives and the incidence of myocardial infarction, we examined whether factor V Leiden, a recently identified genetic marker related to thrombosis, was associated with the risk of myocardial infarction among young women; and, whether other factors modified the risk associated with the presence of the factor V mutation (1). We demonstrated that this relatively common prothrombotic genetic abnormality increased the risk of myocardial infarction among young women only in the presence of other risk factors. Below, we summarize the major findings of this study of the determinants of myocardial infarction in young women.

Risk factors related to myocardial infarction in young women

As expected, older age, current cigarette smoking, obesity, hypercholesterolemia, hypertension, diabetes, family history of premature myocardial infarction, and post-menopausal (surgically menopausal) status were strongly associated with the risk of incident myocardial infarction among the young women (Table 1). Of note, 75 percent of the women who experienced a myocardial infarction were current smokers and 58 percent were obese. The prevalence of current use of low-dose estrogen oral contraceptives was lower among the cases than the controls; and, current use of low-dose estrogen oral contraceptives was not associated with an increased risk of myocardial infarction overall or among older pre-menopausal women, current smokers, or women with other risk factors, including obesity, hypercholesterolemia, hypertension, and diabetes. The presence of the factor V Leiden mutation, factor V R506Q, was higher among the women who suffered a myocardial infarction (9.5%) compared to controls (4.1%) (Table 2). After adjustment for age, factor V Leiden was associated with a 2.4 fold increase in the risk of myocardial infarction. Further restriction of the sample to caucasian women, pre-menopausal women, or women not using oral contraceptives altered only slightly the age-adjusted odds ratio associated with the presence of factor V Leiden. After further adjustment for current smoking, obesity, hypercholesterolemia, hypertension, and diabetes, the presence of factor V Leiden was associated with a four-fold increase in the risk of myocardial infarction (1).

The increased risk of myocardial infarction associated with the presence of factor V Leiden was observed only among current cigarette smokers (Table 3). Among women who did not smoke, factor V Leiden was not associated with an increased risk of myocardial infarction; and, among women who smoked, factor V Leiden was associated with a 3 fold increase in the risk of myocardial infarction. Compared to women who did not smoke and did not carry the factor V Leiden mutation, women who both smoked and carried the

Table 1. Characteristics of MI patients and control subjects

	Patients with MI (n=79)	Controls (n=388)
Age (yr)		
Mean	39.7	37.2
Median	41.0	39.0
Range	23 - 44	19 - 44
Ethnicity (%)		
White, not Hispanic	87.3	89.1
African American	6.3	2.3
Other	6.3	8.6
Current smokers (%)	74.7	22.4
Obesity (%)	58.2	27.0
Hypertension (%)	34.2	9.5
Hypercholesterolemia (%)	41.8	15.7
Diabetes mellitus (%)	15.2	2.8
Post-menopausal (%)	32.9	11.1
Current oral contraceptive use (5)	5.1	10.6
First degree relative risk history of MI (%)	54.4	29.8
Frequency of vigorous exercise (%)		
≥ 3 times/week	7.7	24.2
Some but < 3 times/week	23.1	39.8
None	69.2	35.9

Table 2. Factor V Leiden among MI patients and control subjects

	Patients with MI (n=79)	Controls (n=388)
Factor V Leiden (AG)	8 (9.5)	16 (4.1)
Factor V wild type (GG)	71 (90.5)	372 (95.9)

Table 3. Factor V Leiden and current smoking: separate and combined effects on MI

Current smoking	Factor V Genotype	Patients with MI (n=79)	Controls (n=388)	OR[1]	CI 95%
no	Wildtype	19	288	1	(0.2 - 10.2)
no	Leiden	1	13	1.3	(5.2 - 16.9)
yes	Wildtype	52	84	9.4	(7.0 -128.2)
yes	Leiden	7	3	29.9	

[1] All odds ratios are age-adjusted and are relative to the reference category: those who did not smoke and did not carry the mutation.

Table 4. Factor V Leiden and obesity: separate and combined effects on MI

Obesity[1]	Factor V Genotype	Patients with MI (n=79)	Controls (n=388)	OR[2]	CI 95%
no	Wildtype	29	267	1	
no	Leiden	4	14	2.5	(0.8 - 8.0)
yes	Wildtype	42	102	3.7	(2.2 - 6.3)
yes	Leiden	4	2	19.3	(3.3 -111.5)

[1] Obesity defined as present if BMI $\geq$ 27.5.
[2] All odds ratios are age-adjusted and are relative to the reference category: those who were not obese and did not carry the mutation.

mutation had a 30 fold increase in their risk of myocardial infarction.

The risk of myocardial infarction associated with obesity also was modified by the factor V Leiden mutation (Table 4). In the absence of the mutation, obesity was associated with a 4 fold increase in the risk of myocardial infarction. However, obesity was associated with an 19 fold increase in the risk of myocardial infarction in the presence of factor V Leiden. Of note, each of the 4 non-obese women who were carriers of the factor V Leiden mutation and experienced a myocardial infarction were current smokers.

Similarly, the presence of one or more metabolic risk factors, including obesity, hypercholesterolemia, hypertension, and diabetes, altered the risk associated with the presence of factor V Leiden (Table 5). In the absence of these factors, factor V Leiden was not associated with an increased risk of myocardial infarction. Compared to women who had none of these risk factors and who did not have factor V Leiden, the presence of one or more of these metabolic risk factors was associated with a five fold increase in the risk of myocardial infarction in the absence of factor V Leiden and a 22 fold increase in risk in the presence of factor V Leiden. In short, the presence of factor V Leiden increased the risk among women with one or more metabolic risk factor by four fold.

Table 5. Factor V Leiden and metabolic risk factors: separate and combined effects on MI

Risk Factors[1]	Factor V Genotype	Patients with MI (n=79)	Controls (n=388)	OR[2]	CI 95%
none	Wildtype	14	208	1	(0 - 6.7)
none	Leiden	0	11	0	(2.7- 9.4)
one or more	Wildtype	57	161	5.0	(6.4-77.5)
one or more	Leiden	8	5	22.2	

[1] Either obesity (BMI $\geq$ 27.3) or diagnosed hypercholesterolonemia, hypertension, diabetes, or combination of these factors.
[2] All odds ratios are age-adjusted and are relative to the reference category: those who did not have any of these four risk factors and did not carry the mutation.

Discussion

Because of the small number of patients with myocardial infarction and the low prevalence of factor V mutant gene carriers, the preliminary findings summarized above should be considered as hypothesis generating rather than hypothesis testing. The statistical power to detect interactions in the study was limited; and, the clustering of risk factors limited the ability to examine combinations of factors separately. Nevertheless, the findings summarized above suggest that among young women factor V Leiden carriership was associated with an increased risk of myocardial infarction only when other risk factors are present. Current smoking and metabolic risk factors were strongly associated with the risk of myocardial infarction among women who did not carry the factor V mutant gene, however, the risk associated with these factors was increased markedly in the presence of the mutant prothrombotic gene.

We explored whether the risk associated with factor V Leiden, a prothrombotic factor, was altered by current smoking, in part, because early studies of users of high dose estrogen oral contraceptives suggested that among smokers there was a large increase in the risk of myocardial infarction, possibly because of a prothrombotic effect of oral contraceptives (11,12). As expected, the prevalence of current smoking was 22 percent among controls; and, urrent smoking was strongly associated with the risk of myocardial infarction among young women. While cigarette smoking was associated with an increased risk of myocardial infarction in the absence of factor V Leiden, the presence of the mutation increased the already higher risk among current smokers three fold. Whether other prothrombotic mutations in coagulation factors, such as a recently identified prothrombotic mutation in factor II, also interact with cigarette smoking and increase substantially the risk of myocardial infarction among young women remains unknown (44).

We also explored whether a prothrombotic risk factor, factor V Leiden, altered the risk associated with atherosclerotic risk factors, including obesity, hypercholesterolemia, hypertension, and diabetes. The combined prevalence of one or more of the atherosclerotic risk factors among controls was 44 percent; and, the presence of one or more of these risk factors was strongly associated with the risk of myocardial infarction. As noted above, the presence of factor V Leiden increased the risk associated with the presence of one or more of the metabolic risk factors by four fold.

Both atherosclerosis and thrombosis contribute to the occurrence of myocardial infarction among the young (as well as latter in life). With the identification of the genetic mutations related to the physiologic abnormalities that lead to familial thrombophilia, there now is the opportunity to explore potential interactions of atherogenic and prothrombotic risk factors in the etiology of myocardial

infarction. In the Physicians Health Study, factor V Leiden was not associated with the incidence of myocardial infarction (43). However, the Physicians Health Study focused on male physicians, aged 40-84 years; and, among the participants, there were low prevalences of current smoking and other risk factors and high prevalences of factors related to a healthy lifestyle, such as regular exercise and moderate alcohol consumption. It also is unclear whether the findings related to factor V Leiden observed in the population-based study among young women summarized above should be generalized to older women and men.

Since few cases of myocardial infarction among young women (<5%) occurred among non-smokers who were free of other risk factors for coronary heart disease, efforts to identify factors that increase the risk among those with other risk factors is of particular importance. As we suggest, these efforts may identify persons at particularly high risk of myocardial infarction as a result of the joint effects of a genetic predisposition to thrombosis and risk factors for atherosclerosis. Of even greater importance, the investigation of interactions between prothrombotic factors and other determinants of myocardial infarction among the young may provide clues to potential interactions that contribute to the occurrence of myocardial infarction latter in life.

The occurrence of myocardial infarction is multi-causal. In addition to heritable factors, lifestyle factors, such as diet, exercise, and smoking, contribute to the risk of myocardial infarction. The effects of these behaviors may be mediated, in part, through effects on the levels or activity of factors related to coagulation, fibrinolysis, or platelet function or these factors may modify the effects of hemostatic factors. Additionally, these and other factors, such as infection with chlamydia pneumonae, herpes simplex Type 1, and cytomegalovirus, may alter coronary vessel walls and plaque stability, and, thereby, increase the risk of athero-thrombotic disease.

Recently, attention has focused on events that might trigger the occurrence of myocardial infarction (45). As in venous thrombosis, it is unlikely that acute myocardial infarction occurs spontaneously. In the presence of both atherosclerosis and a prothrombotic factor, a triggering event may precipitate an acute myocardial infarction. For example, it is possible that prothrombotic factors influence the risk of exercise-related myocardial infarction among middle-aged men with atherosclerosis (46).

Additional observational studies are needed to explore potential interactions between behavioral factors (smoking, diet, and physical activity), metabolic factors (obesity, hypercholesterolemia, hypertension, and diabetes) and common prothrombotic genetic mutations. Future research should examine interactions between atherogenic risk factors and newly identified prothrombotic mutations. DNA poly-morphisms that result in physiologic consequences related to thombosis are not altered by other risk factors, subclinical coronary artery disease, or the occurrence of myocardial infarction. For this reason, retropective population-based case control studies can be used to examine potential interactions in low-risk populations, such as young women and men.

Summary

Myocardial infarction in the young provides a unique model for the investigation of potential interactions between atherosclerotic and prothrombotic risk factors. Because myocardial infarction reflects athero-thrombotic disease, it is important to take into account factors related to atherosclerosis when examining prothrombotic factors as potential determinants of myocardial infarction. In Western societies, there are increases in both the prevalences of metabolic risk factors and atherosclerotic coronary disease with aging. The clinical expression of the thrombotic risk associated with heritable factors, such as factor V Leiden, as myocardial infarction appears to occur only in the presence of other risk factors, such as smoking and known metabolic risk factors related to atherosclerosis.

If confirmed in other studies of factor V Leiden and with other mutations related to prothrombotic risk, these observations will likely have both etiologic and practical consequences. Finally, we suggest that efforts to determine whether a prothrombotic risk factor contributes "independently" to the risk of myocardial infarction may lead to a significant underestimation of the importance of the factor in the occurrence of myocardial infarction, particularly among clinically-important subsets of the population.

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