Relationship Between Intermittent Claudication, Inflammation, Thrombosis, and Recurrent Cardiac Events Among Survivors of Myocardial Infarction

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Background: Among coronary disease patients, concomitant peripheral arterial disease is a potent risk factor for future cardiac events and mortality. We sought to determine clinical and biochemical markers that might better elucidate the relationship between coronary and peripheral arterial disease.

Methods: Two months after an index myocardial infarction, 1045 patients provided detailed medical histories and underwent blood testing for selected hemostatic, lipid, and inflammatory markers. Patients were then followed up prospectively for a mean of 26 months.

Results: Compared with individuals without intermittent claudication (n=966), those with claudication (n=78) (information was unavailable for 1 individual) were significantly older and demonstrated an increased frequency of diabetes mellitus, tobacco use, prior cardiac and cerebrovascular events, and depressed left ventricular function. Individuals with claudication were less likely to receive β-blocker therapy after the index infarction. Individuals with claudication had evidence of enhanced procoagulant and proinflammatory states manifested by relative elevations in plasma fibrinogen, D-dimer, C-reactive protein, and serum amyloid A concentrations. During follow-up, the presence of claudication was associated with an independent 2-fold increase in the combined end point of death or nonfatal cardiac event (38.5% vs 17.8%, P = .001) and a 5-fold increase in cardiac mortality (19.2% vs 3.6%, P = .001). Patients with intermittent claudication who were not treated with β-blockers had a significant 3-fold mortality excess relative to those receiving β-blockers.

Conclusions: Following myocardial infarction, the added presence of intermittent claudication is associated with heightened procoagulant and proinflammatory states and an underuse of β-blocker therapy and is a strong independent predictor of recurrent cardiovascular events.

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THEROSCLEROSIS IS A SYSTEMIC DISORDER WITH A PROPENSITY TO AFFECT MULTIPLE VASCULAR BEDS. THE PRESENCE OF LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE, WHETHER SYMPTOMATIC OR CLINICALLY SILENT, IS ASSOCIATED WITH SIGNIFICANTLY ELEVATED RISK FOR FUTURE CARDIAC EVENTS AND MORTALITY.1-4 EVEN AMONG PATIENTS IN WHOM CORONARY ARTERY DISEASE HAS ALREADY BECOME CLINICALLY MANIFEST, THE ADDITIONAL PRESENCE OF PERIPHERAL ARTERIAL DISEASE PORTENDS WORSE OUTCOMES.3,5-8 WHETHER THE COEXISTENCE OF PERIPHERAL ARTERIAL DISEASE IN CORONARY DISEASE PATIENTS SIMPLY DENOTES A MORE ADVANCED STAGE IN THE DISEASE PROCESS OR INSTEAD REFLECTS A DIFFERENT, PERHAPS MORE AGGRESSIVE, UNDERLYING PATHOPHYSIOLOGIC PROCESS IS UNCLEAR. IN AN ATTEMPT TO BETTER UNDERSTAND THE RELATIONSHIP BETWEEN CORONARY AND PERIPHERAL ARTERIAL DISEASE, THE PRESENT STUDY EXAMINED DIFFERENCES IN CLINICAL VARIABLES; MEDICAL THERAPIES; LEVELS OF MULTIPLE THROMBOGENIC, LIPID, AND INFLAMMATORY FACTORS; AND PROGNOSIS WITHIN A LARGE COHORT OF POSTINfarCTION PATIENTS WITH AND WITHOUT COEXISTING INTERMITTENT CLAUDICATION.

METHODS

STUDY POPULATION

This investigation is a substudy of the Thrombogenic Factors and Recurrent Coronary Events (THROMBO) study.9 One thousand forty-five patients were enrolled 2 months after an index myocardial infarction between October 3, 1994, and June 30, 1997. Patients of either sex who were 21 years or older and had been admitted to a coronary care unit at 1 of 13 participating hospitals with a documented acute myocardial infarction (enzyme-confirmed with symptoms or electrocardiographic changes) and who survived until 2 months after the index event were eligible for enrollment. Full de-
tails regarding enrollment and exclusion criteria are outlined in the primary publication.9

At the time of enrollment, a detailed medical history and listing of current medications were recorded. The presence or absence of intermittent claudication, defined clinically as the occurrence of exertion related calf, hip, or buttock discomfort that occurred with walking and was relieved with rest, was determined at the time of study entry. Patients were followed up prospectively (mean, 26 months) for the occurrence of study end points.

THROMBOGENIC, LIPID, AND INFLAMMATORY FACTORS

Blood samples were obtained in the fasting state at the time of study enrollment, 2 months after the index myocardial infarction. The patients were advised not to take their morning medications and to refrain from smoking within 24 hours prior to blood draw. Oral anticoagulant therapy (warfarin sodium) was not withheld. Following blood draws, plasma was immediately separated by centrifugation and transferred into 1-mL cryovial containers. All specimens were stored at –80°C and transferred to designated core laboratories.

Specific assays for thrombogenic factors (D-dimer, fibrinogen, von Willebrand factor, factor VII, factor VIIa, and plasminogen activator inhibitor 1) and metabolic factors (cholesterol, triglycerides, high-density lipoprotein cholesterol, lipoprotein[a], and apolipoproteins A1 and B) were performed using previously published methods, as indicated in the primary study publication.9 Low-density lipoprotein cholesterol was calculated via the Friedewald equation. C-reactive protein (CRP) and serum amyloid A (SAA) levels were measured using high-sensitivity assays.10

END POINT DATA

Primary end points for the THROMBO study were defined as death due to coronary heart disease or recurrent nonfatal myocardial infarction, whichever occurred first.

Secondary end points were defined as death due to coronary heart disease or recurrent nonfatal myocardial infarction or unstable angina pectoris, whichever occurred first. The association between intermittent claudication and death also was analyzed.

STATISTICAL ANALYSIS

Baseline clinical characteristics and levels of blood variables were compared between individuals with and without intermittent claudication using the χ² test, t test (2-tailed, unpaired), and nonparametric Mann-Whitney test, where appropriate. Multivariate logistic regression analysis was used to determine the association between hematologic variables and peripheral arterial disease after adjustment for clinical covariates and medications. Odds ratios describe the likelihood of the patient with peripheral arterial disease having a blood level of the tested variable in the high-risk quartile. The effect of the presence or absence of intermittent claudication on the time to cardiac events was assessed using the Kaplan-Meier method and the log-rank test. The Cox proportional hazards survivorship method (SAS Institute, Cary, NC) was used to determine whether peripheral arterial disease was independently associated with cardiac events after adjustment for the clinical covariates and medications listed in Table 1.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Intermittent claudication was present in 78 patients (7.5%), whereas 966 denied symptoms of claudication (information regarding intermittent claudication status was unavailable for 1 subject). Compared with individuals without intermittent claudication, those with claudication were significantly older, more frequently had diabetes mellitus, and were more likely to be current or previous smokers (Table 1). The groups did not differ in relation to sex, race, and prevalence of hypertension. Patients with claudication were more likely to have experienced prior cardiac symptoms (angina pectoris), have had a prior cardiovascular event (stroke or prior myocardial infarction), and exhibit left ventricular dysfunction (as measured by a history of pulmonary congestion and an ejection fraction ≤30%) than subjects without claudication.

Patients with and without intermittent claudication did not differ with respect to frequency of treatment with aspirin, lipid-lowering agents, or warfarin. Patients with claudication, however, were significantly less likely to receive β-blocker therapy than patients without claudication. Conversely, calcium channel antagonists, nitrates, and angiotensin-converting enzyme inhibitors were more commonly prescribed among patients with intermittent claudication.
Evidence of a heightened thrombotic state was present among patients with claudication, as reflected by significantly elevated concentrations of fibrinogen and D-dimer and by nonsignificant trends toward increased concentrations of all other hemostatic factors that were examined (Table 2). Even after exclusion of patients taking warfarin at the time of enrollment, concentrations of these factors remained significantly greater among individuals with claudication. Among patients who were not receiving warfarin therapy, levels of factor VII (but not factor VIIa) were significantly higher in patients with vs without claudication (P = .02).

Relative to the post–myocardial infarction group without claudication, patients with intermittent claudication demonstrated a significant increase in concentrations of the inflammatory markers CRP and SAA. There was no significant difference in concentrations of lipids between individuals with and without intermittent claudication.

The association between peripheral arterial disease and levels of blood variables also was tested in a multivariate logistic regression after adjustment for clinical covariates. Advanced age (P = .02), diabetes mellitus (P < .001), prior myocardial infarction (P < .001), smoking (P = .004), and pulmonary congestion (P = .002) were significantly associated with the presence of claudication. After adjustment for these clinical variables, elevated levels of fibrinogen (odds ratio, 2.10; P = .005), D-dimer (odds ratio, 1.75; P = .046), and CRP (odds ratio, 2.41; P = .002) remained significantly associated with intermittent claudication. von Willebrand factor levels did not maintain significance after adjustment (odds ratio, 1.22; P = .47).

## CARDIAC END POINTS

During the mean follow-up of 26 months, patients with claudication were 5 times more likely than those without claudication to have a fatal cardiac event (19.2% vs 3.6%; P = .001) and more than twice as likely to have any major adverse cardiac event (38.5% vs 17.8%; P = .001). Kaplan-Meier analysis demonstrated an early and progressively separation of the time-to-event curves for all adverse events based on the presence or absence of intermittent claudication (Figure 1).

Given the more extensive cardiac risk factor profile, increased incidence of prior cardiovascular events, and relative decrease in left ventricular function observed among individuals with intermittent claudication, Cox proportional hazards multivariate analysis was performed to determine if intermittent claudication was associated with adverse outcomes independent of these potentially confounding clinical variables. After adjustment for the clinical variables listed in Table 1, the presence of intermittent claudication remained associated with a significantly and independently elevated risk of future cardiac events and mortality (Table 3). Among all clinical variables examined, intermittent claudication was the most potent predictor of future adverse cardiac events. This association was not altered by medication variables added one at a time to the models. Likewise, the presence of intermittent claudication remained an independent predictor of nonfatal infarction or death during follow-up after adjustment for differences in inflammatory and hemostatic markers (hazard ratio, 2.51; P < .001).

Because β-blocker use might have affected the clinical course of patients, we evaluated the cumulative probability of cardiac events among patients with intermittent claudication in relationship to β-blocker use. As shown in Figure 2, patients with claudication who were not treated with β-blockers had a significantly higher mortality than those who received β-blocker therapy.

## COMMENT

Among a large group of individuals who survived a recent myocardial infarction, the added presence of intermittent claudication is associated with significantly enhanced thrombotic and inflammatory states, as evidenced by increased levels of fibrinogen, D-dimer, CRP, and SAA protein. In addition, postinfarction patients with intermittent claudication were significantly less likely than individuals without claudication to receive β-blocker therapy, despite data suggesting significant survival benefits among patients with claudication who were treated with β-blockers (Figure 2).
Concordant with prior reports, a strong independent relationship was found in our cohort between the presence of intermittent claudication and the risk of subsequent major adverse cardiac events. Compared with patients without intermittent claudication, those with claudication were significantly older, more likely to have diabetes mellitus and a history of smoking, and more often had a history of prior cardiovascular events, severe left ventricular dysfunction, and pulmonary edema. Even after adjustment for these factors, intermittent claudication remained a strong predictor of cardiac events, including cardiac death and nonfatal reinfarction. In summary, our findings suggest that an association exists between the heightened prothrombic and proinflammatory states observed among postinfarction patients with claudication and adverse outcomes in this subset.

PERIPHERAL ARTERIAL DISEASE AND CARDIAC EVENTS

Among patients with symptomatic peripheral arterial disease, long-term outcomes are poor relative to matched controls.²⁻⁴ In a study of 2777 male veterans with claudication followed up for a mean duration of 47 months, an annual mortality of 12% was observed, which was significantly greater than that of the age-adjusted US male population.² Two thirds of deaths in this cohort were attributable to cardiac disease. In a separate population-based study⁵ of 8843 men aged 40 to 65 years, intermittent claudication was associated with an independent 1.5-fold increase in all-cause mortality during a 21-year follow-up. Poor outcomes have also been noted among patients with coronary artery disease and peripheral atherosclerosis, the latter serving as a harbinger of adverse cardiac events and mortality among individuals with clinically stable coronary disease,⁶ those undergoing coronary bypass surgery,⁷ and those presenting with myocardial infarction.⁷⁻⁸ Within our cohort of clinically stable survivors of a recent myocardial infarction, the added presence of symptomatic peripheral arterial disease was associated with a greater than 2-fold excess of recurrent nonfatal coronary events and a greater than 5-fold increase in cardiac death during the ensuing 26 months.

HEMATOLOGIC MARKERS OF THROMBOSIS AND INFLAMMATION

A large body of evidence derived from clinical, pathologic, and in vitro analyses has implicated thrombosis and inflammation as critical components of coronary arterial plaque rupture and its attendant clinical sequelae. In population-based studies,¹²⁻¹⁶ blood levels of hematologic markers, including fibrinogen, D-dimer, von Willebrand factor, and tissue plasminogen activator, and serum concentrations of markers of inflammation, including CRP and SAA protein, correlate with the presence or subsequent development of clinically overt coronary heart disease. In addition, among apparently healthy men, baseline levels of fibrinogen and CRP are independent predictors of the future development of symptomatic peripheral arterial disea.

Figure 1. Cumulative probability of cardiac events in postinfarction patients with and without peripheral arterial disease (PAD), defined based on symptoms of intermittent claudication. A, Secondary cardiac events, defined as unstable angina or nonfatal myocardial infarction or cardiac death. B, Primary cardiac events, defined as nonfatal myocardial infarction or cardiac death. C, Cardiac events, defined as cardiac death (P<.001 for all, log-rank statistic).

Elevated serum concentrations of different inflammatory and thrombotic factors have been shown among various patient populations to correlate with future adverse cardiovascular events.⁹⁻¹⁰ In our study population of patients after myocardial infarction, the additional presence of intermittent claudication was associated with significantly increased concentrations of fibrinogen, D-dimer, and CRP. Therefore, while patients with coronary disease exhibit a heightened tendency toward thrombosis and inflammation relative to healthy controls, patients with symptomatic coronary and peripheral arterial disease demonstrate further alterations in thrombotic and inflammatory markers. Interestingly, no significant differences in lipid factors were observed between patients with and without peripheral arterial disease regardless of lipid-lowering therapy. Lack of differences in lipid profiles between patients with and without symptomatic peripheral arterial disease could be explained by the atherosclerotic enrichment of our overall population consisting exclusively of postinfarction patients.

Although postinfarction patients with concurrent symptomatic peripheral arterial disease demonstrated elevated serum levels of selected inflammatory and thrombotic markers relative to postinfarction patients without coexisting claudication, the issue of “cause and effect”
remains uncertain. Specifically, it is unclear from our study whether a heightened inflammatory and thrombotic state among individuals with coronary artery disease predisposes to the development of peripheral arterial disease, or is merely a reflection of more diffuse atherosclerosis that has already developed.

Among post–myocardial infarction patients enrolled in our study, elevated D-dimer levels together with elevated apolipoprotein B and lower apolipoprotein A levels were independent predictors of primary cardiac events after adjustment for clinical predictors of adverse events. Interestingly, in our study population, while fibrinogen and CRP were predictive of future primary cardiac events in a univariate model, these factors did not emerge as independent predictors of primary cardiac events in a multivariate model that included other clinical predictors of adverse outcomes, including the presence of intermittent claudication. Most important, the presence of claudication remained independently associated with adverse cardiac events after adjusting for elevated D-dimer, elevated apolipoprotein B, and lower apolipoprotein A levels.

INTERMITTENT CLAUDICATION AND β-BLOCKER THERAPY

Randomized clinical trials have demonstrated that β-adrenergic receptor antagonist administration following myocardial infarction is associated with significant reductions in early and late mortality.21-23 In our study population, only about half of the myocardial infarction survivors with symptomatic peripheral arterial disease were receiving β-blocker therapy 2 months following their index event, a proportion that was significantly less than that observed among patients without claudication. The reasons for this more limited use of β-blocker therapy among postinfarction patients with claudication are likely multifactorial. Because of concerns that β-blocking agents may further reduce blood flow through diseased peripheral arteries, the presence of claudication has been viewed as a relative contraindication for this form of therapy.24 More recent studies,25,26 however, suggest that β-blockers do not reduce peripheral perfusion or adversely affect walking capacity in patients with intermittent claudication and are, in fact, well tolerated in these individuals. Given the adverse prognostic implications of peripheral arterial disease following myocardial infarction, coupled with the known survival benefits of β-blocker therapy, individuals with peripheral arterial disease might be expected to benefit especially from this form of therapy. In our postinfarction patients with intermittent claudication, those treated with β-blocker therapy experienced a 3-fold reduction in cumulative cardiac mortality, compared with patients not treated with β-blockers.

LIMITATIONS

The diagnoses of myocardial infarction and intermittent claudication were based on clinical definitions. While the study used standard criteria to define the presence of intermittent claudication, routine confirmatory lower extremity arterial testing (ankle-brachial indexes and duplex ultrasonography) was not performed. Although the presence of intermittent claudication correlates well with the presence of underlying arterial obstructive disease, other nonvascular syndromes can produce leg pain and may have been present among some patients considered to have claudication.

CONCLUSIONS

The present study provides further evidence that in postinfarction patients symptomatic peripheral arterial disease is associated with worse outcomes. Individuals with concomitant intermittent claudication and coronary artery disease demonstrated hematologic evidence of height-
ended thrombotic and inflammatory states compared with patients with coronary disease alone. Postinfarction patients with intermittent claudication were also less likely to receive β-blocker therapy, despite the survival benefits of this therapy. In addition to emphasizing the need for the more appropriate use of β-blocker therapy in this high-risk group, these findings also raise the question as to whether therapies specifically targeted at thrombosis (such as clopidogrel bisulfate) or at inflammation may have a special role in these patients.

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Error in Table. In the Review Article by Messerli et al titled “Do Thiazide Diuretics Confer Specific Protection Against Strokes?” published in the November 24, 2003, issue of the ARCHIVES (2003;163:2557-2560), in Table 2 on page 2559, the comparative treatment for the ALLHAT Study should have read “Chlorthalidone vs amlodipine.”