Risk Factors for Progression of Peripheral Arterial Disease in Large and Small Vessels

Victor Aboyans, MD, PhD; Michael H. Criqui, MD, MPH; Julie O. Denenberg, MA; James D. Knoke, PhD; Paul M Ridker, MD, MPH; Arnost Fronek, MD, PhD

Background—Data on the natural history of peripheral arterial disease (PAD) are scarce and are focused primarily on clinical symptoms. Using noninvasive tests, we assessed the role of traditional and novel risk factors on PAD progression. We hypothesized that the risk factors for large-vessel PAD (LV-PAD) progression might differ from small-vessel PAD (SV-PAD).

Methods and Results—Between 1990 and 1994, patients seen during the prior 10 years in our vascular laboratories were invited for a new vascular examination. The first assessment provided baseline data, with follow-up data obtained at this study. The highest decile of decline was considered major progression, which was a −0.30 ankle brachial index decrease for LV-PAD and a −0.27 toe brachial index decrease for SV-PAD progression. In addition to traditional risk factors, the roles of high-sensitivity C-reactive protein, serum amyloid-A, lipoprotein(a), and homocysteine were assessed. Over the average follow-up interval of 4.6±2.5 years, the 403 patients showed a significant ankle brachial index and toe brachial index deterioration. In multivariable analysis, current smoking, ratio of total to HDL cholesterol, lipoprotein(a), and high-sensitivity C-reactive protein were related to LV-PAD progression, whereas only diabetes was associated with SV-PAD progression.

Conclusions—Risk factors contribute differentially to the progression of LV-PAD and SV-PAD. Cigarette smoking, lipids, and inflammation contribute to LV-PAD progression, whereas diabetes was the only significant predictor of SV-PAD progression. (Circulation. 2006;113:2623-2629.)

Key Words: diabetes mellitus ■ inflammation ■ lipoproteins ■ peripheral vascular disease ■ smoking

The cumulative findings on molecular and cellular biology have dramatically changed our concept of atherosclerotic disease. Data suggest different pathways for its initiation and progression, which in turn are different from those triggering acute cardiovascular disease (CVD). Even though atherosclerosis is a multifocal disease, the risk factors contributing to its development in different organs (ie, the heart, brain, or limbs) and different segments (proximal and distal vessels) are not identical. Since the discovery of major risk factors for atherosclerotic CVD, some newer risk factors have the potential to improve specific algorithms for CVD risk estimation. Among them, acute-phase inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and serum amyloid-A (SAA) and other substrates such as lipoprotein(a) [Lp(a)] and homocysteine (Hcys) present a high level of evidence for association with atherosclerotic CVD. Whether these factors contribute to the initiation and/or progression of the atherosclerotic process requires further investigation. Additionally, conflicting results have opened debate on the role of inflammation on small-vessel disease physiopathology in different arterial territories.

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In this longitudinal study, we assessed the role of traditional and selected novel risk factors on the progression of peripheral arterial disease (PAD), with a special focus on potential differences on predictors of large-vessel (LV) and small-vessel (SV) PAD progression. We hypothesized that the factors contributing to PAD progression differ in large and small vessels.

Methods

Study Population
Patients were recruited from 1990 to 1994 from those seen in the prior 10 years for a noninvasive lower extremity arterial testing at the San Diego VA Center or the University of California, San Diego Medical Center vascular laboratories (the Figure). Among the 2265 potential candidates, 481 were deceased, 1276 could not be located.
or declined the invitation, and 508 patients returned for a new, comprehensive, noninvasive vascular examination of the lower limbs, as well as an assessment of their CVD risk factors with a standard questionnaire, a clinical examination, and a fasting blood sample for further analyses. Data for these 508 patients have been compared with those abstracted at baseline in 77 survivors randomly selected among those declining the invitation or those not located. The participants had slightly less advanced PAD according to noninvasive tests but were otherwise comparable.

All participants signed a consent form approved by the University of California, San Diego Institutional Review Board. Data from all previous vascular laboratory examinations were recorded. Except for those undergoing interval lower-limb arterial revascularization procedures, results from the new assessment performed were considered follow-up. For those having revascularization at any time before this study, an intervention-free period was determined. In this instance, at least 2 series of vascular testing were required, and follow-up values corresponded to those obtained immediately before revascularization.

Eighty-five patients with no intervention-free period were excluded from this analysis. We also excluded 20 subjects with an ankle brachial index (ABI) elevation exceeding 0.15 in both legs, because an ABI increase of this extent is beyond what can be considered the measurement variability. In this situation, arterial stiffening, which could conceal PAD progression, was suspected.

In total, we assessed PAD progression on 403 subjects. This article presented in the study population.

Vascular Assessment

ABI and TBI were obtained after blood pressure measurement on ankles, big toes, and arms by the phymognomonometric technique. The signals were detected by photoplethysmography at the big toes and the third fingers. Because of the known association between subclavian stenosis and PAD,17 the higher brachial systolic pressure was used for the ABI and TBI denominator. The reproducibility of these 2 tests has been reported. The 95% CI of ABI has been reported to range from 0.10 to 0.15.18–20 TBI variability is estimated to be from the same to about twice that of the ABI.21 The baseline and follow-up ABI and TBI were restricted to a maximum of 1.15 to avoid bias from falsely high pressures related to stiffened arteries.

Blood Parameters

Blood cholesterol and triglycerides assays were performed on the Abbott VP “superystem” bichromic enzymatic analyzer. The cholesterol assay used Boehringer-Manheim’s high-performance cholesterol reagent, whereas the triglycerides assay used Abbott’s A-Gent reagent and a lipase-free version to determine the free glycerol blank. The HDL cholesterol procedure used heparin–manganese chloride as a precipitant. The hs-CRP assay was performed by an ultrasensitive immunotechnique on the Behring BNII analyzer (Dade Behring, Newark, Del). The SAA and Lp(a) assay was performed by an immunotechnique on the Behring BNII analyzer (Dade Behring). Total Hcy was measured by high-performance liquid chromatography with fluorometric detection using reagents from BioRad Laboratories (Hercules, Calif).

Assessment of PAD Progression

We assessed the ABI decline as a marker of LV-PAD progression. Major LV-PAD progression was defined as the highest 10% of ABI decline.

We assessed the TBI decline as a marker of SV-PAD progression. Because TBI change could be affected by the progression of PAD proximally, we excluded patients with an ABI decrease exceeding −0.15 (113 patients). Thus, the analysis on SV-PAD progression was performed on a subset of 290 subjects, with an ABI change within the −0.15 to 0.15 range. Significant SV-PAD progression was defined as the highest 10% of TBI decline.

Statistical Analysis

According to the distribution of ABI change during the follow-up period, the top 10th percentile of ABI decrease corresponded to an ABI drop exceeding −0.3, defining a significant PAD progression. This binary definition has been entered as the dependent variable in a logistic regression model. Baseline ABI was included in the model to avoid regression to the mean. Other independent variables studied were age, follow-up duration, sex, history of diabetes (self-reported and/or according to laboratories files and/or taking antidiabetic drugs), current smoking at follow-up (versus nonsmokers and past smokers, the latter defined as having stopped smoking >1 year ago), heavy drinking (>21 alcohol beverages per week), ratio of total to HDL cholesterol, triglycerides, body mass index, systolic and diastolic blood pressures, and pulse pressure. As in the univariate analysis, pulse pressure presented a more significant predictive value than diastolic blood pressure; the latter has been replaced by the former because the 3 variables (systolic, diastolic, and pulse pressure) could not be simultaneously added in the model. Triglycerides, hs-CRP, SAA, Lp(a), and Hcy values were natural log-transformed as a result of skewed distribution. Results also were adjusted for use of antihypertensive, antithrombotic, and lipid-lowering drugs.

Similarly, a logistic regression model was run for SV-PAD progression, with the presence or absence of a TBI drop exceeding −0.27 (the 10th percentile of TBI change distribution) as the dependent variable. Baseline TBI and baseline and follow-up ABI values were systematically added in the model to adjust TBI changes to those possible resulting from ABI upstream. Other independent variables were similar to those entered in the LV-PAD model. The final models presented were obtained after a stepwise procedure stopped when all factors presented a value of P=0.20. Age, sex, systolic blood pressure, and drug therapies were systematically included. Data were analyzed with StatView 5.0 (SAS Institute, Cary, NC) statistical software.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

General Data

The population consisted of 351 men and 52 women (Table 1). The prevalence of an ABI <0.9 at baseline was at 44.9%. The mean period of follow-up was at 4.6±2.5 years.
TABLE 1. Study Population (n=403): Demographics and Distribution of Potential Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence or Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.63±9.03</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>351 (87.1)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic whites</td>
<td>348 (86.4)</td>
</tr>
<tr>
<td>Blacks</td>
<td>26 (6.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>19 (4.7)</td>
</tr>
<tr>
<td>Others</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>113 (28.04)</td>
</tr>
<tr>
<td>Past smokers, n (%)</td>
<td>225 (55.83)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>46.0±41.1</td>
</tr>
<tr>
<td>Excessive alcohol, n (%)</td>
<td>19 (4.71)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>150 (37.22)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>142.0±22.0</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.9±9.7</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>64.1±19.9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5±8.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>207.6±40.7</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>46.2±13.3</td>
</tr>
<tr>
<td>Ratio of total to HDL cholesterol</td>
<td>4.79±1.42</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>163.0±116.4</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>5.8±7.9</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td>1.09±3.07</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>20.4±24.9</td>
</tr>
<tr>
<td>Hcy, mg/L</td>
<td>14.2±11.0</td>
</tr>
<tr>
<td>Antihypertensive therapy, n (%)</td>
<td>238 (59.1)</td>
</tr>
<tr>
<td>Lipid-lowering medication, n (%)</td>
<td>85 (21.1)</td>
</tr>
<tr>
<td>Antithrombotics, n (%)</td>
<td>235 (58.3)</td>
</tr>
</tbody>
</table>

LV-PAD Progression

A significant decrease in ABI (P<0.0001) occurred during follow-up (Table 2). In patients with data on both legs available, an ABI change was noted as follows: 118 patients (29%) had a bilateral ABI decrease, 92 (33%) presented a bilateral ABI increase, and 69 patients (17%) had a divergent ABI evolution. We compared 43 patients with an ABI decrease exceeding −0.3 with the remaining 360 subjects. The mean ABI change in the leg with the greatest progression was −0.43±0.13 in the former group versus 0.04±0.10 in the reference group (P<0.0001). The LV-PAD progression models are displayed in Table 3. Among traditional risk factors, current smoking and ratio of total to HDL cholesterol were independent and significant predictors of LV-PAD progression. Diabetes was not predictive, whereas pulse pressure and heavy drinking were borderline predictors. Among the novel risk factors, Lp(a) and hs-CRP were predictive. We did not find any interaction between hs-CRP and antithrombotic therapy (data not shown).

SV-PAD Progression

During the follow-up period, a significant decrease in TBI (P<0.03) occurred (Table 2). We compared the 29 subjects with a TBI decrease exceeding −0.27 with the other 261 subjects. In the former group, the mean TBI change in the leg with the greatest TBI decrease was −0.41±0.12 compared with 0.02±0.15 in the reference group (P<0.0001). The baseline ABI of the corresponding leg was not significantly different between those with and without SV-PAD progression (0.90±0.25 versus 0.93±0.21, respectively; P=0.47). The ABI change between both groups was not significantly different (−0.01±0.08 versus −0.03±0.07; P=0.44). Table 4 displays the initial and final models for SV-PAD progression. Diabetes was the only significant predictor of SV-PAD progression.

Additional models were run with ABI and TBI change as continuous dependent variables (data not shown). These models produced quite similar findings.

Discussion

In this longitudinal study, we confirmed the hypothesis that the contributing factors for LV and SV disease progression are different. The subsequent analyses of ABI and TBI changes in this report are in line with earlier data of a cross-sectional study in another cohort, suggesting different risk factors for prevalent LV-PAD and SV-PAD. Nonetheless, unlike that study in which no correlates with prevalent isolated SV-PAD were found, our data show the unique role of diabetes in the progression of this condition in an ≈5-year follow-up.

An ABI decrease of <−0.3 is a stringent criterion for LV-PAD progression, substantially exceeding the ABI measurement variability. The ABI is considered a marker of LV disease because it may reflect disease not only in the calf arteries but also in proximal larger arteries.

Similarly, our SV-PAD progression criterion of TBI decrease exceeding −0.27 (without any significant ABI change) greatly surpasses its measurement variability range. A TBI drop without significant ABI change is related to the progression of disease in foot arteries with a diameter <3 mm.

We preferred a dichotomous definition of LV-PAD and SV-PAD progression, which can be clinically considered substantial. The −0.06 mean decrease in ABI during ≈5 years (−0.012/y) is much higher than the −0.025/5 y decrease observed in a general population and comparable to the −0.014/y decrease observed in a cohort of claudicants. In our study, 28% of patients presented an ABI decrease exceeding −0.15, similar to the 30% observed after 5 years in a contemporary cohort of vascular surgery patients. However, our analysis is the only one that excluded legs with a high level of ABI increase (0.15). In light of recent publications on the prognostic significance of high ABIs, we decided to exclude legs with a significant ABI increase because this condition differs from the atherosclerotic pro-
Among traditional risk factors, current smoking appeared to be the most powerful predictor of LV-PAD progression. These data, based on objective measurements, are in line with the majority of studies but not all studies on the clinical progression of PAD. Smoking cessation is considered a first-line treatment among smokers with PAD. Our data are supported by those in the Cardiovascular Health Study, in which smoking was the strongest predictor of ABI decline.

Unlike smoking status, diabetes, considered the other major risk factor for PAD, affects mostly smaller vessels. With postexercise ABI change used as a progression criterion, an earlier study did not find significant progression related to diabetes. Similarly, diabetes was not a significant predictor of ABI decline in the Cardiovascular Health Study. Surgical series have already described diabetes-related PAD particularities, affecting predominantly distal arteries, with lesser revascularization possibilities and higher amputation rates. Furthermore, diabetes affects limb arteries 2 ways: by promoting atherosclerotic occlusive disease and by arterial wall stiffening related to medial calcinosi. Despite the exclusion of legs with high ABIs and high ABI increases, we cannot exclude that in some legs, a parallel progression in arterial stiffening would not mask a development of occlusive disease, leading to a “pseudonormal” ABI with TBI decrease. It is well known that ABI is an imperfect marker of lower limb perfusion in diabetics and that the TBI measurement should always be associated.

Experimental models provide compelling evidence for the role of inflammation in the initiation, progression, and complication of atherosclerosis, confirmed in the clinical setting. High levels of hs-CRP are correlated with angiographic coronary artery disease progression, and the hs-CRP decrease under statins was inversely correlated with the rate of coronary artery disease progression assessed by intravascular ultrasound. However, another study failed to show any relationship between hs-CRP and coronary artery calcium progression. In the peripheral vasculature, both hs-CRP and SAA are related to the progression of atherosclerosis in carotid arteries. Our data suggest a predictive role for hs-CRP in the progression of LV-PAD. Data on PAD in the literature are scarce. The occurrence of symptomatic PAD is related to the hs-CRP level. In the Walking and Circulation Study, hs-CRP was associated with low ABI only in the case of coexistent CVD. In patients with severe PAD, hs-CRP is strongly predictive of fatal and nonfatal cardiovascular outcomes. At an asymptomatic level, van der Meer et al showed a significant progression of radiographically detected iliac calcified deposits and a borderline ABI decrease in the top-quartile plasma hs-CRP group. The Edinburgh Artery Study underlined the role of several inflammatory markers, including hs-CRP, in the ABI decrease over a period of 12 years, with an independent predictive role for interleukin-6, which was not assessed in our study.

We did not find any correlation between hs-CRP and SV-PAD progression, which conflicts with the Rotterdam...
To the best of our knowledge, this is the first study on the survival prognosis of the Hcys-PAD association. Through investigations of the relationship between inflammation and arteriosclerosis, the authors also proposed alternative hypotheses for this association as opposed to a direct relationship. However, the authors also proposed alternative hypotheses for this association as opposed to a direct relationship.

Several previous studies on Hcys and PAD progression are surprising. In a surgical series, Hcys was related to a higher ABI decrease as compared to the normal group, suggesting different biological pathways. In vitro studies report a different type of acute-phase response than hs-CRP. Unlike the finding for hs-CRP, we did not find any significant results for SAA. This difference merits further investigation because SAA has been suggested to represent a different biological pathway than hs-CRP.

Our study failed to show any relationship between Hcys and PAD progression. Although the relationship between elevated Hcys and prevalent PAD has been documented, studies on Hcys and PAD progression are surprising. In a surgical series, Hcys was related to a higher ABI decrease but was not predictive for further revascularization or amputation. There is no evidence of any effect on PAD progression after Hcys levels are decreased with folates and vitamin B6 supplementation. One explanation would be the severe survival prognosis of the Hcys-PAD association.

Through different biological pathways, in vitro studies report increased thrombogenicity with higher Hcys levels, suggesting that the main deleterious effect of Hcys would be related to acute thrombotic events rather than atherosclerosis progression.

Lp(a) already has been shown to be independently associated with prevalent PAD and inversely correlated with ABI. To the best of our knowledge, this is the first study with an objective quantification reporting the role of Lp(a) in PAD progression.

The study population consisted of those patients who had survived, could be located, and were willing to participate. Thus, progression in our study group was likely an underestimate because of the occurrence of death before enrollment of some subjects with fast-evolving atherosclerotic disease. A limitation of our study is that it is unknown whether this conservative estimate of progression had an impact on effect size estimates for risk factors, although the power probably was reduced.

It should be emphasized that the number of subjects included in the SV-PAD progression analysis was lower than those included in the LV-PAD progression analysis, leading to lower statistical power. The reason is that we had to exclude those with a substantial ABI decrease to detect SV-PAD progression specifically. A larger number of subjects might have revealed Lp(a) as a significant factor; Lp(a) showed a similar hazard ratios for LV-PAD and SV-PAD progression (P<0.20 in the SV-PAD progression model).

In conclusion, in this cohort of vascular laboratory subjects with or without PAD, we confirmed the role of active smoking and ratio of total to HDL cholesterol in the progression of LV-PAD and provide new data on the importance of Lp(a) and hs-CRP as new markers of PAD progression affecting large vessels. The progression of SV-PAD was related only to diabetes, suggesting different pathophysiology for the progression of PAD in large and small vessels.

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Disclosures

Dr Ridker is listed as a coinventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in CVD. The other authors report no conflicts.

References

In this longitudinal study of 403 vascular laboratory patients, we evaluated risk factors for large-vessel–peripheral artery disease (LV-PAD) progression, defined as the highest decile of decline in the ankle brachial index, exceeding −0.30, as well as small-vessel–PAD (SV-PAD) progression, defined as the highest decile of decline in the toe brachial index, exceeding −0.27, the latter in a subgroup of 290 patients with a relatively stable ankle brachial index (ankle brachial index change within the −0.15 to 0.15 range). During a mean follow-up of 4.6 years, risk factors for PAD progression differed in large and small vessels. In multivariable analysis, current smoking, ratio of total to HDL cholesterol, lipoprotein(a), and high-sensitivity C-reactive protein were related to LV-PAD progression, whereas only diabetes was associated with SV-PAD progression. These results highlight the importance of standard and novel cardiovascular risk factors in PAD progression in larger vessels but also demonstrate the apparent singular role of diabetes in atherosclerotic progression in smaller vessels. Clinically, the findings here are consistent with observational studies showing the benefit of smoking cessation and the documented efficacy in clinical trials of therapy for dyslipidemia in retarding LV-PAD progression and further suggest that lipoprotein(a) and high-sensitivity C-reactive protein might be additional therapeutic targets. However, they also suggest that treatment of diabetes may be the key to retardation of SV-PAD progression.
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