The generalized nature of atherosclerosis: how peripheral arterial disease may predict adverse events from coronary artery disease

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Abstract: Non-invasive measurements, especially segmental pressure ratios and flow measurements, are useful for gauging the severity of peripheral arterial disease (PAD). Although the incidence of PAD is similar for men and women, men are more likely to have severe disease, while women usually have more moderate or asymptomatic disease. Published reports confirm the clinical impression that patients with PAD are more likely to have both coronary artery disease and cerebrovascular disease than those without PAD. However, the degree of overlap is a function of the sensitivity of the diagnostic assessments for the three conditions. A San Diego population study found that the incidence of PAD may be underestimated, with many patients being asymptomatic. Based on blood flow measurements, the study found that 11.9% of the study population had large vessel PAD. Morbidity from both coronary heart disease and stroke was increased in people with PAD, who were 2.5 times more likely to present with morbidity from cardiovascular disease (CVD) than those who did not have PAD. Several studies have now confirmed the strong predictive value of PAD for subsequent CVD mortality and that the risk of CVD mortality increases with the severity of PAD.

Key words: atherosclerosis; cardiovascular disease; coronary heart disease; non-invasive testing; peripheral arterial disease

Introduction

Atherosclerotic disease is common in older adults, and causes significant morbidity and mortality in this group. Peripheral arterial disease (PAD) is an obstructive disease in the lower limbs, and patients with atherosclerosis of the leg arteries are likely to have pathologically similar lesions in other vascular beds. Indeed, PAD has proved to be a sensitive marker for other forms of atherosclerosis, such as cerebrovascular disease and coronary artery disease. Accurate assessment of PAD could be useful in preventing further atherosclerotic morbidity and mortality by providing an early indication of the need for intervention.

The San Diego population study

Patients with PAD are sometimes asymptomatic or have atypical symptoms; thus, many estimates of PAD prevalence greatly underestimate the true numbers. To determine the true prevalence of PAD, a population was examined using several non-invasive techniques for evaluating large- and small-vessel PAD.[1] The study population was a subset of residents from a predominantly white, free-living, upper-middle-class city in southern California who were originally studied under a Lipid Research Clinics protocol.[2] Medical histories were obtained and physical examinations were performed on 624 adults ranging from 38 to 82 years of age, with a mean age of 66 years. In addition, a battery of non-invasive tests was performed to measure the blood flow in their lower limbs, including segmental pressures and flow measurements in the femoral and posterior tibial arteries. These measurements were used to define the subjects' PAD status. Information was obtained on the PAD status of 565 subjects. Of these, 67 (11.9%) had large-vessel peripheral arterial disease (LV-PAD), as defined by abnormal segmental pressures or flow abnormalities. Ninety subjects (15.9%) had isolated small-vessel peripheral arterial disease (ISV-PAD), as defined by an abnormal toe pressure ratio or a prolonged toe pulse reappearance half-time with normal proximal tests. Using this assessment, 408 subjects (72.2%) did not have PAD.

Co-prevalence of PAD and CVD

Focusing only on those subjects who did not have PAD or who presented with LV-PAD, the authors looked at the association of PAD with other cardiovascular diseases (CVD), defined as coronary artery disease or cerebrovascular disease. Baseline CVD was defined as a medical history of myocardial infarction (MI), coronary artery bypass graft surgery (CABG), stroke, or surgery for stroke prevention. These data were used to analyze the co-prevalence of PAD with other manifestations of CVD.

Among men, 10 of 34 subjects (29.4%) with PAD also had CVD, whereas only 21 of 183 men (11.5%) who did not have PAD manifested CVD; the results were similar for women (Table 1). Overall, the probability that patients with PAD also manifested CVD was 25.4%, whereas the probability of having CVD in the absence of PAD was only 10.3%. Thus, CVD occurs approximately 2.5 times more

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Table 1 Cross-sectional overlap between non-invasively determined LV-PAD and CVD[a] among a population of older subjects (mean age of 66 years) from San Diego, USA.

	CVD		
	Present	Absent	Total
PAD in men			
present	10	24	34
absent	21	162	183
total	31	186	217
PAD in women			
present	7	26	33
absent	21	204	225
total	28	230	258

Overall: presence of CVD in patients with PAD = 17/67 (25.4%); presence of CVD in patients without PAD = 42/408 (10.3%).
[a]CVD history of MI, CABG, stroke, or stroke surgery.

often in people with PAD than in those without PAD, even when patient recall was the only method of obtaining a medical history to identify CVD.[3]

Dormandy and colleagues reviewed a number of clinical studies that examined the prevalence of coronary artery disease in patients with leg ischemia.[4] Although most investigators screened patients for coronary disease with a medical history and a resting electrocardiogram, a few used treadmill or other stress ECG, dipyridamole stress thallium imaging, or angiography. When only a medical history and the resting ECG were used, between 20% and 50% of patients with PAD as a presenting symptom were found to have evidence of coronary artery disease. When stress tests or angiography were used, coronary artery disease could be found in 60–90% of the patients with PAD. Thus, most patients with PAD have evidence of coronary artery disease. The exact clinical correlation depends on how carefully and meticulously disease is looked for.

Dormandy and colleagues also looked at the prevalence of cerebrovascular disease in patients with PAD.[4] In this instance, use of only the clinical history of CVD resulted in prevalence values for PAD ranging from a low of 0.5% to a high of 15%. Here again, with more sensitive tests such as assessments of cervical bruits with Doppler ultrasonography evaluation of the carotids, evidence of cerebrovascular disease was found in 45–50% of patients with PAD. These results support the concept that atherosclerosis is a generalized disease, and it is again clear that the degree of co-prevalence found depends on the thoroughness of the evaluation.

PAD and CVD morbidity

The literature on PAD and its association with other morbid events is rather sparse. Therefore the authors looked at baseline morbidity, incident morbidity, and total morbidity from both coronary artery disease and stroke in individuals who either had LV-PAD or were normal at baseline in this study.[5] Both baseline and total coronary disease rates were elevated in men with LV-PAD, and both baseline and total stroke rates were dramatically higher for men with LV-PAD than for those who did not have LV-PAD at baseline (Figure 1). The data were similar for women (Figure 2).[5]

A few studies have looked at combined morbidity and mortality among patients with PAD. A Swedish study defined PAD as an ankle–brachial index (ABI) of less than 0.9; among patients with PAD by this definition, the combined incidence of fatal and non-fatal cardiac events was about 2.5 times greater than in those without the disease.[6] In the Systolic Hypertension in the Elderly Program (SHEP) study, an adjusted relative risk of 2.5 was found when CVD morbidity and mortality were examined in subjects with and without PAD, defined as an ABI $\leqslant 0.9$.[7] All of the subjects in SHEP had isolated systolic hypertension and had been randomized into a study of antihypertensive therapy.

PAD and mortality

Intermittent claudication (IC) alone, despite its limited sensitivity and specificity for PAD assessed by non-invasive testing,[8] increases the likelihood of CVD mortality. Reunanen showed that IC independently contributed to coronary and cardiovascular mortality.[9] Using age- and sex-matched populations of normal individuals and patients with IC, Jelnes tracked subject survival for over 7 years. Mortality among patients with IC was 44%, about twice that of the controls.[10] The increased rates of mortality in patients with IC indicate that PAD is an important factor to consider when evaluating cardiovascular disease, since it appears to serve as a surrogate marker for the severity of atherosclerotic disease.

In the authors' population study, men were somewhat more likely to present with LV-PAD than women, with the rates being approximately 13% and 11%, respectively. However, differences between the sexes in the severity of disease were more marked. As can be seen in Table 2, men were more than twice as likely to have severe disease (ABI $\leqslant 0.6$), whereas women were more likely to manifest blockage of the posterior tibial artery despite a normal ABI (isolated posterior tibial disease), a less severe condition that is typically asymptomatic.[8]

Data were combined from men and women in the population study to look at the relative risk of death among subjects with LV-PAD compared with normal subjects over a 10-year follow-up period.[3] Data were adjusted for possible confounders, including age, sex, cigarette use, blood pressure, high- and low-density lipoprotein cholesterol levels, logarithm of the triglyceride level, glucose and body mass index. Findings indicated relative risks of about 3 for total mortality and about 6 for cardiovascular and coronary disease mortality. After excluding subjects with baseline CVD, defined as previous MI, CABG, stroke or stroke surgery, the relative risk dropped somewhat for coronary disease (to about 4), but was relatively stable for CVD. This indicates that LV-PAD is a significant and independent contributor to CVD mortality.

Subjects with ISV-PAD were also examined and it was found that coronary death was about 2.6 times more likely among the 90 subjects with this condition.[11] As a caveat, this condition is poorly defined because it is difficult to correlate with angiographic findings. Further, it has been found in clinical studies that these individuals are a heterogeneous group, since some people with ISV-PAD experience dynamic changes in blood flow. For example, during one examination a subject may have a low toe pressure or a long pulse reappearance half-time, while these may be normal at the next examination. In about one-third of subjects, however, ISV-PAD was a precursor to LV-PAD. The

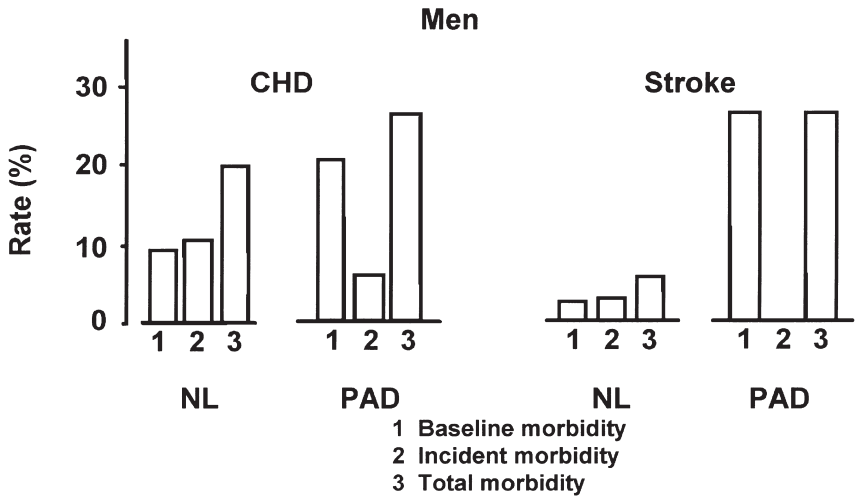

Figure 1 Rate of morbidity and mortality from coronary heart disease (CHD) and stroke in normal males and males with LV-PAD (NL, normal).

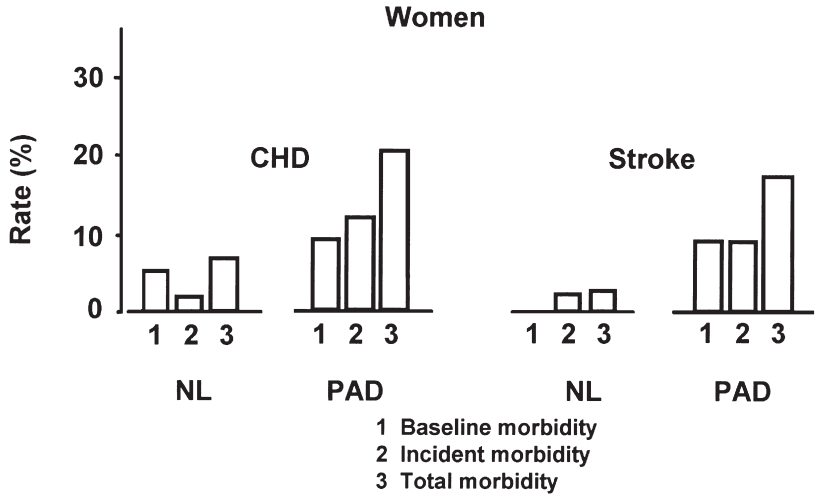

Figure 2 Rate of morbidity and mortality from coronary heart disease (CHD) and stroke in normal females and females with LV-PAD (NL, normal).

Table 2 Severity of PAD among men and women (mean age of 66 years) from San Diego, USA, 1985.

PAD category	Women		Men	
	n	%	*n*	%
Normal	225	72.8	183	71.5
ISV-PAD	51	16.5	39	15.2
IPT	18	5.8	13	5.1
Moderate	9	2.9	9	3.5
Severe	6	1.9	12	4.7
IPT + moderate + severe		10.7		13.3
Total	309	100.0	256	100.0

ISV-PAD, isolated small-vessel PAD; IPT, isolated posterior-tibial PAD; moderate, ankle–brachial index 0.6–0.9; severe, ankle–brachial index ⩽0.6.

changes measured were consistent and stable in this latter group, and over time these patients developed low ABI scores.[12]

In examining 13 years of follow-up mortality data, a gradation of survival with the severity of disease was found (Figure 3). The trends were similar for both genders, although CVD death rates were higher in men. Subjects with ISV-PAD also had elevated CVD mortality in comparison with normals. Subjects with isolated posterior tibial disease (IPT) or an ABI between 0.6 and 0.9 (moderate disease) experienced approximately a 40% CVD mortality over the 13 years. Men with severe disease (ABI $\leqslant$ 0.6) had greater than 60% CVD mortality, whereas women with severe disease had greater than 30% CVD mortality.

Several hospital-based studies have examined the relationship between PAD and survival in patients who have experienced myocardial infarction. In the SPRINT study in Israel, in-hospital survival, but not post-discharge survival, was significantly reduced in patients with PAD.[13] In contrast, Pardaens and colleagues in Belgium found that

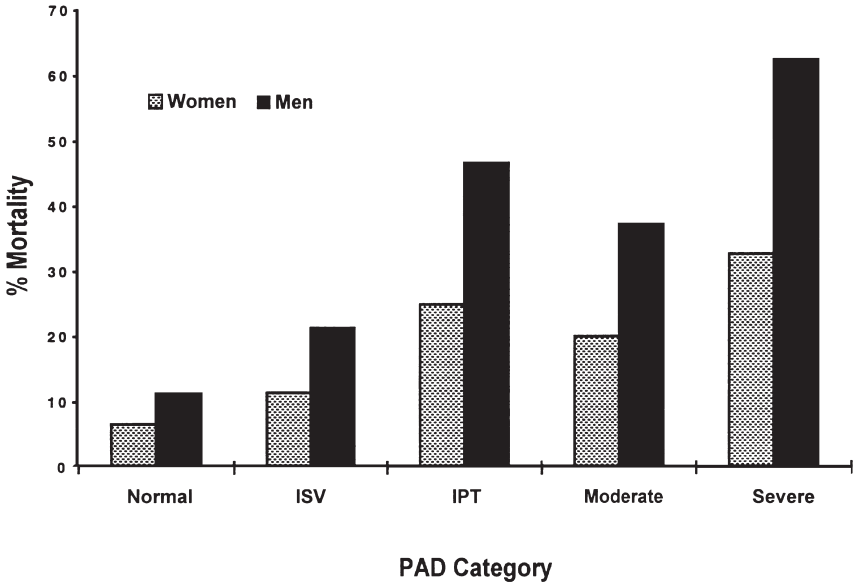

Figure 3 Age-adjusted mortality from CVD and severity of PAD (ISV, isolated small-vessel PAD; IPT, isolated posterior-tibial PAD; moderate PAD, ankle–brachial index 0.6–0.9; severe PAD, ankle–brachial index <0.6).

long-term survival after discharge was significantly reduced by the presence of peripheral vascular disease.[14]

In Pittsburgh, Vogt and colleagues examined survival among women between 1986 and 1992 and found a graded correlation with the ABI.[15] Women with an ABI of 0.9 or less had higher mortality rates than those whose ABI scores were above 0.9. The relative risk of CVD mortality for those women with the lower ABI values was 4.0, even after adjusting for baseline CVD and other risk factors, indicating that a low ABI was an independent risk factor for CVD death.

In a study of men and women referred to a vascular clinic, McKenna also found a graded effect of ABI on survival.[16] The 10-year survival estimates among those patients with an ABI of less than 0.4 was only 33%, while the group with ABI scores ranging from 0.4 to 0.85 had a survival rate of 51%, and three out of four patients with an ABI greater than 0.85 survived 10 years. Thus, data virtually identical to the San Diego study confirm that patients with PAD have a dramatic reduction in survival.

CVD events within a group of PAD patients

A large, multicenter, clinical trial performed in Italy enrolled 2111 patients with PAD who were examined to identify predictors of cardiovascular events.[17] The data were analyzed as a prospective, observational, epidemiologic study, with adjustment for treatment category. Factors that increased the risk of cardiovascular events in patients with PAD in multivariate analysis were evaluated. Hypertension, a low ABI and cigarette smoking independently increased the risk of cardiovascular events, as did a history of vascular surgery, which can be considered as a marker of disease severity. Interestingly, both the white blood cell count and plasma fibrinogen levels were also independently predictive of cardiovascular events in these PAD patients.

Conclusions

Overall, the evidence indicates that patients with PAD have a sharply increased risk of morbidity and mortality from events occurring in either the cerebrovascular or the coronary vascular systems. In particular, the ABI is a highly sensitive indicator of PAD and is relatively simple to assess. Thus, screening patients over 50 years of age using the ABI may be a cost-effective procedure, even if they have no evidence of CVD, since a low ABI points to an increased risk for cardiovascular events. Information about an individual's PAD status is important in planning various risk factor interventions. Data from clinical trials show that the greatest benefits from interventions are achieved in individuals with higher risk, and in particular, in those who already have evidence of atherosclerotic disease.

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