Noninvasively diagnosed peripheral arterial disease as a predictor of mortality: results from a prospective study

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ABSTRACT Intermittent claudication has been reported in previous studies to approximately double the risk of subsequent mortality. However, a history of claudication is often present in the absence of significant peripheral arterial disease (PAD) and absent in the presence of PAD. For this reason we evaluated the association between large-vessel and small-vessel PAD, measured by highly reliable and valid noninvasive tests, and mortality in 567 older subjects from a defined population followed-up for an average of 4 years. Large-vessel PAD was strongly and significantly predictive of all-cause mortality in both men and women with a relative risk of 4 to 5, and this finding was independent of other cardiovascular disease risk factors in multivariable analysis. In addition, this finding persisted after exclusion of subjects with extant cardiovascular disease at baseline. The associations of both claudication and abnormal peripheral pulses with mortality were weaker than the large-vessel PAD association. Isolated small-vessel PAD was unrelated to subsequent mortality. These findings suggest older subjects of both sexes at a high risk of impending mortality can be identified through noninvasive testing for large-vessel PAD.

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IT IS well recognized that the atherosclerotic process is frequently generalized, affecting vessels in various parts of the body. Previous reports have noted the strong association between coronary heart disease and peripheral arterial disease (PAD) and the similarity of risk factors, particularly cigarette smoking and diabetes, for both diseases. Concordant with these observations, the symptomatic expression of PAD, intermittent claudication, has been noted to be predictive of mortality in previous studies, with an approximate doubling of risk. However, after adjustment for risk factors and signs and symptoms of coexisting coronary heart disease, this risk tends to be reduced, suggesting claudication may not be an independent marker for mortality.

It is evident that considerable “noise” is present in such analyses, since in population studies, many subjects who report typical symptoms of claudication may not have PAD and many subjects with PAD have atypical or no symptoms. In a population-based study of older subjects, we used highly reliable and accurate noninvasive techniques to measure PAD, and here report the mortality experience of subjects with and without noninvasively measured PAD after 4 years of follow-up. We also analyzed the prognostic significance of claudication and pulse palpation for mortality as compared with noninvasive testing.

Methods All 624 subjects were residents of a geographically defined community initially studied under a Lipid Research Clinics (LRC) protocol that involved two evaluations, visit 1 and visit 2. At visit 2, about half of the subjects were from a random sample of the LRC visit 1 cohort and the others were selected from the visit 1 cohort for hyperlipidemia, defined as being at or above age- and sex-specific 90th percentiles for cholesterol or 95th percentiles for triglycerides or taking lipid-lowering medications. The PAD study involved a subset of visit 2 subjects, and the PAD subjects were comparable to visit 2 subjects with regard to age, sex, and the proportion with hyperlipidemia (47.9%). Subjects were from a predominantly white, upper-middle-class community in San Diego, and informed consent was obtained after the procedures had been fully explained.

Fifty-seven subjects (9.1%) were excluded from these analyses because of missing data or unreliable noninvasive testing results. Two hundred and fifty-seven men and 310 women ran-
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ing in age from 38 to 82 years with an average age of 66 years remained.

**Criteria for PAD measurements**

**Intermittent claudication.** Claudication was assessed by the standard Rose Questionnaire developed at the London School of Hygiene and Tropical Medicine. Claudication was defined by the Rose criteria: exercise calf pain not present at rest relieved within 10 min only by rest. We also defined as “possible” claudication, exercise calf pain not present at rest but otherwise not fully concordant with the Rose criteria. The remaining subjects, including subjects with leg pain at rest and subjects with exercise pain not including the calf, were categorized as not having claudication.

**Pulse palpation.** On 508 (89.6%) of the subjects, a single examiner performed a standardized bilateral palpation of the femoral, posterior tibial, and dorsalis pedis arteries with pulses subjectively graded from 0 to 4, and auscultation of the groin for femoral bruits. Pulses lower than grade 3 or audible bruits were considered abnormal. This examination was done before noninvasive testing, and the examiner was unaware of the subject’s responses to the claudication questionnaire.

**Noninvasive testing.** Four different noninvasive measurements of limb perfusion in the lower extremities were made: segmental blood pressure, flow velocity, postocclusive reactive hyperemia, and pulse reappearance half-time.

**SEGMENTAL BLOOD PRESSURE.** The ratio of arm systolic blood pressure to pressure at five different levels of the lower extremity (upper thigh, above knee, below knee, above ankle, and toe) were recorded by the sphygmomanometric technique and a mercury-in-Silastic gauge attached to the toe.

**FLOW VELOCITY.** The Doppler effect produced by back-scattered ultrasound from red blood cells in motion was used to measure flow velocity in the femoral and posterior tibial arteries.

**POSTOCCLUSIVE REACTIVE HYPEREMIA.** The phenomenon was used to mimic exercise blood flow requirements. Arterial flow was halted by inflating a cuff below the knee to a suprasystolic value for 4 min. Upon release of the cuff, the Doppler flow velocity response (reactive hyperemia) was recorded from the femoral artery. The percentage increase above baseline as well as the time for the response to return to 50% of peak were recorded.

**PULSE REAPPEARANCE HALF-TIME.** Simultaneously with the postocclusive reactive hyperemia test, the pulse reappearance half-time, or time it took after releasing the cuff for the pulse amplitude to reach one-half the baseline value, was recorded.

**Large-vessel PAD.** Large-vessel PAD was defined as either an abnormal segment-to-arm blood pressure ratio ($LV_{BP}+$) or an abnormal large-vessel flow velocity ($LV_{FV}+$).

$LV_{BP}+$ was defined as

- (both an above ankle and below knee ratio $\leq 0.8$)
- an above and below knee ratio $\leq 0.8$, and
- a lower ankle ratio $\leq 0.7$
- an above knee ratio $\leq 0.8$
- an upper thigh ratio $\leq 0.8$

$LV_{FV}+$ was defined as either a

- (femoral peak forward flow of $\leq 20$ cm/sec)
- (a femoral pulse decay of $\geq 260$ msec or
- (a femoral deceleration of $\leq 100$ cm/sec$^2$)
- a posterior tibial pulse decay of $\geq 220$ msec or
- a posterior tibial deceleration of $\leq 70$ cm/sec$^2$

Although these tests measure dynamic aspects of perfusion rather than the degree of anatomic obstruction, they have been demonstrated to have a very high correlation with moderate or larger vessel PAD determined angiographically.

**Small-vessel PAD.** Small-vessel PAD was defined by an isolated toe pressure abnormality or a pulse reappearance half-time abnormality or a combination of abnormalities in pulse reappearance half-time, postocclusive reactive hyperemia, and time for hyperemic response to fall to 50% of peak. Specifically, the presence of small-vessel PAD was defined as

- (a toe ratio $\leq 0.7$ with the above ankle ratio and the below knee ratio normal)
- (a pulse reappearance half-time $\geq 20$ sec)
- (a pulse reappearance half-time $\geq 15$ sec and a postocclusive reactive hyperemia $\leq 75\%$ and time for hyperemic response to fall to 50% of peak $\geq 40$ sec)

The cutpoints chosen represent extreme values from previous studies of normal control subjects. Because small-vessel PAD cannot be reliably assessed angiographically, anatomic correlation of these tests is impractical.

**Surgery for PAD.** Subjects were asked whether they had ever had surgery for poor circulation to the extremities, other than for varicose veins, and the nature and location of the surgery. Subjects with documented surgery for PAD underwent the noninvasive testing along with other subjects. For this analysis, surgical subjects were arbitrarily considered to have had large-vessel PAD.

**Covariates.** Age at last birthday and past and current cigarette smoking were determined by questionnaire. Pack-years was chosen as the smoking variable, rather than current smoking, because of both the low prevalence of current smokers in this older population and the possibility of selective cessation of smoking in ill individuals. A past history of angina, myocardial infarction, or stroke were also determined by questionnaire.

Blood pressure was measured in the sitting position with a random zero sphygmomanometer. High-density (HDL), low-density (LDL), and very low-density (VLDL) lipoprotein cholesterol levels were measured by standardized LRC Program methods.

**Dependent variables.** The dependent variable was all-cause mortality during an average follow-up time of approximately 4 years. The study population is surveyed routinely on an annual basis as part of an ongoing LRC follow-up study, and reported deaths are confirmed by obtaining death certificates. The underlying cause of death on each death certificate was determined, but the small number of deaths (30) precluded cause-specific multivariable analyses.

**Statistical analysis.** Sex-specific, unadjusted death rates by claudication, pulse palpation, and PAD categories, as well as simple relative risks, were calculated. Two categories of PAD were evaluated: large-vessel PAD, with or without concomitant small-vessel PAD, and isolated small-vessel PAD, both compared with subjects free of any PAD. The category of isolated small-vessel PAD was defined because of the possibility that small-vessel PAD accompanying large-vessel PAD might reflect, to some degree, reduced small-vessel flow as a result of proximal stenoses in larger vessels. Adjustment for covariates, including age, was performed with the Cox proportional hazards model, which calculates the statistical significance for each variable in the model and which also adjusts for differences in follow-up time for deceased subjects. Subjects with isolated
small-vessel PAD were excluded from Cox models evaluating the risk of large-vessel PAD and subjects with large-vessel PAD were excluded from Cox models evaluating the risk of isolated small-vessel PAD.

Results

Table 1 shows the sex-specific and combined crude mortality rates in subjects with large-vessel PAD or isolated small-vessel PAD vs subjects with normal results of noninvasive testing. Sixty-nine of 567 subjects (12.2%) had large-vessel PAD, and an additional 90 (15.9%) had isolated small-vessel PAD. The overall death rate was 30 of 567 (5.3%). However, 14 of the 69 subjects with large-vessel PAD (20.3%), died in the follow-up period compared with five of the 90 subjects with isolated small-vessel PAD (5.6%) and 11 of the 408 (2.7%) subjects without PAD, giving crude relative risks of mortality of 7.5 for large-vessel PAD and 2.1 for isolated small-vessel PAD. Although death rates were lower overall in women (3.2% vs 7.8% in men), the relative risk for large-vessel PAD for death was, if anything, greater in women (8.2 vs 6.8 in men).

Table 2 shows that the preponderance of deaths were cardiovascular in the groups with large-vessel PAD and isolated small-vessel PAD, whereas among subjects with normal findings the majority of deaths were from cancer. The numbers of deaths were too small for reliable inference concerning cause-specific mortality. However, the crude relative risk of large-vessel PAD for cardiovascular death (11.8), was much greater than the relative risk for cancer (4.2).

Table 3 presents relative risks for Rose claudication, Rose or possible claudication, and abnormal pulse examination (defined as a femoral bruit or a diminished or absent femoral or posterior tibial pulse). For all subjects the relative risk for Rose claudication was 1.9, which improved to 3.7 when possible claudication was added. The relative risk for abnormal pulse examination was similar at 3.4. However, each of these values were less than half the relative risk for noninvasively measured large-vessel PAD.

To distinguish the extent to which the large-vessel PAD mortality association was confounded by, alternatively, age and sex, the traditional cardiovascular disease risk factors, or extant cardiovascular disease at baseline, three sets of Cox models were run.

Table 4 shows the first set of Cox model results with only age, sex, and large-vessel PAD entered as predictor variables. A decade of aging independently increased the risk of death about 69% and men were at about twice the risk of women. Both results were of borderline statistical significance. However, large-vessel PAD was powerfully and independently predictive of mortality, with a relative risk of 5.23 (95% confidence interval = 2.28 to 12.02, p = .0001). A Cox model with isolated small-vessel PAD, age, and sex entered as predictor variables (not shown) revealed no independent statistically significant association of isolated small-vessel PAD with mortality.

The left-hand column in table 5 shows for all subjects, the statistical significance for large-vessel PAD and for each of the covariates in the second set of Cox models. After controlling for HDL, LDL, VLDL, systolic blood pressure, and pack-years of cigarette smoking in addition to age and sex, the association between large-vessel PAD and mortality decreased only slightly, with a relative risk of 4.23 (95% confidence interval = 1.80 to 9.97, p = .001), indicating little

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality rates and relative risks in men and women with large-vessel PAD or isolated small-vessel PAD compared with normal subjects</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Men (n)</td>
</tr>
<tr>
<td>Deaths (n)</td>
</tr>
<tr>
<td>% Deaths</td>
</tr>
<tr>
<td>Women (n)</td>
</tr>
<tr>
<td>Deaths (n)</td>
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<tr>
<td>% Deaths</td>
</tr>
<tr>
<td>All subjects (n)</td>
</tr>
<tr>
<td>Deaths (n)</td>
</tr>
<tr>
<td>% Deaths</td>
</tr>
</tbody>
</table>

LV-PAD = large-vessel PAD; SV-PAD = small-vessel PAD.
TABLE 2
Distribution of deaths in subjects with large-vessel PAD, isolated small-vessel PAD, and normal findings, and relative risks of large-vessel PAD for cardiovascular and cancer mortality

<table>
<thead>
<tr>
<th></th>
<th>Isolated LV-PAD (n = 69, deaths = 14)</th>
<th>Isolated SV-PAD (n = 90, deaths = 5)</th>
<th>Normal (n = 408, deaths = 11)</th>
<th>Relative risk (LV-PAD/normal)</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>11.8a</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

a(8/69)/(4/408) = 11.8.

b(5/69)/(7/408) = 4.2.

TABLE 3
Relative risks of mortality in men and women with Rose claudication, Rose or possible claudication, or abnormal pulse examination compared with other subjects

<table>
<thead>
<tr>
<th></th>
<th>Rose claudication</th>
<th>Rose or possible claudication</th>
<th>Abnormal pulse examinationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>2.7</td>
<td>4.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td>n</td>
<td>1.9</td>
</tr>
<tr>
<td>All subjects</td>
<td>1.9</td>
<td>3.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>

aAbnormal femoral pulse or blunt or abnormal posterior tibial pulse.

TABLE 4
Relative risks of mortality derived from the Cox model for age, sex, and large-vessel PADa

<table>
<thead>
<tr>
<th></th>
<th>Relative risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 years)</td>
<td>1.69</td>
<td>.05</td>
</tr>
<tr>
<td>Male vs female</td>
<td>1.99</td>
<td>.09</td>
</tr>
<tr>
<td>Large-vessel PAD</td>
<td>5.23b</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Subjects with isolated small-vessel PAD excluded.

95% confidence interval = 2.28 to 12.02.

Discussion

Previous reports have documented that intermittent claudication is a risk factor for mortality,1,3,4 although the independence of this finding has been less certain.5 We hypothesized that if PAD is a marker for subsequent mortality, a much more accurate assessment of PAD should provide a more accurate, and larger, estimate of risk, because misclassification bias would be greatly reduced.10 We have described the prognostic significance in a defined population of accurately assessed large-vessel PAD for mortality and our results have suggested a greater than fourfold excess risk for subjects with large-vessel PAD, independent of other cardiovascular risk factors or disease at baseline.

By contrast, isolated small-vessel PAD was not significantly related to mortality in multivariable analysis. We have recently reported that isolated small-ves-

TABLE 5
Statistical significance in Cox model of large-vessel PAD and all covariates in all subjects and in subjects free of cardiovascular disease at baseline

<table>
<thead>
<tr>
<th></th>
<th>Excluding subjects with history of angina, MI, or stroke at baseline (n = 476, deaths = 25)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large vessel PAD</td>
<td>.001 (RR = 4.23b)</td>
</tr>
<tr>
<td>Age</td>
<td>.07</td>
</tr>
<tr>
<td>Sex</td>
<td>.36</td>
</tr>
<tr>
<td>HDL</td>
<td>.06</td>
</tr>
<tr>
<td>LDL</td>
<td>.35</td>
</tr>
<tr>
<td>VLDL</td>
<td>.02</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>.36</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>.06</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; RR = relative risk; BP = blood pressure.

aSubjects with isolated small-vessel PAD excluded.

b95% confidence interval = 1.80 to 9.97.

c95% confidence interval = 1.74 to 11.69.
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Pulse PAD is also unrelated to claudication, abnormal pulses, sex, hyperlipidemia, or age after age 60.5,6

The risk associated with large-vessel PAD was clearly higher than that for less accurate determinations of large-vessel PAD by claudication or abnormal pulses (table 1 vs table 3). We had expected that PAD would be predictive of higher mortality mainly from atherosclerotic disease. The data in table 2 support this idea, although there was some excess of cancer deaths in the group with large-vessel PAD, perhaps reflecting the powerful effect of smoking on both cardiovascular disease and cancer and/or possibly poorer general health and survival in subjects with large-vessel PAD. Overall, the numbers were too small to draw firm conclusions.

Before our multivariable analysis, we were aware of the well known associations between cigarette smoking and both large-vessel PAD and mortality, and we considered the possibility that large-vessel PAD was simply a marker for cigarette smoking. Thus we were particularly interested in the multivariable analysis to note that the large-vessel PAD—mortality association was largely independent of cigarette smoking, even though cigarette smoking was itself independently associated with mortality. The only other statistically significant result was a positive association for VLDL cholesterol, which was contrary to our expectation since VLDL is essentially a surrogate for triglycerides, which is not thought to be an independent risk factor of cardiovascular disease.20 However, this issue remains controversial, and in our population VLDL was a more important risk factor than LDL for all-cause mortality.

In a previous study from Finland, only a small part of the association between claudication and mortality was attributable to risk factors of cardiovascular disease,7 and our study had a similar result for the large-vessel PAD association with mortality. It thus appears as though the increased specificity in measuring extent atherosclerosis, albeit in the lower extremities, leads to a better prediction of mortality even with simultaneous consideration of multiple risk factors of cardiovascular disease.

In the Finnish study, adjusting for signs and symptoms of coronary heart disease eliminated the independent effects of claudication on mortality, whereas in our study, after exclusion of subjects with angina, myocardial infarction, or stroke at baseline, the relative risk for large-vessel PAD was, if anything, higher. Thus, in our population the prognostic significance of large-vessel PAD for mortality was independent of both risk factors and of extent cardiovascular disease. A recent Swedish study of patients with claudication used venous occlusion plethysmography to diagnose PAD. Patients with positive plethysmographic results had a 2.2 to 4.9 times greater 10 year mortality rate, depending on age, with younger patients having a greater relative risk.21 The increased mortality risk was mainly caused by myocardial infarction. However, the data were not adjusted for other cardiovascular risk factors or disease at baseline.

The relative risk of 4 to 5 of large-vessel PAD for mortality is similar to recent reports of the relative risk of an ischemic exercise electrocardiography test for coronary heart disease morbidity22 or coronary heart disease and cardiovascular disease mortality.23 It should be noted that, unlike exercise electrocardiography, these noninvasive PAD tests require no exertion and are essentially without risk.

In conclusion, the prognostic significance of large-vessel PAD in our population was largely independent of risk factors of cardiovascular disease, and independent of extant cardiovascular disease at baseline. These results suggest that men and women at high risk of impending mortality might be identifiable by noninvasive PAD testing, and thus such testing may alert us to patients who require additional evaluation or who might benefit from additional intervention. We would caution that these results, although highly statistically significant, are based on only 30 deaths. Our follow-up of this population is continuing.

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